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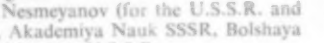

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[1] J. B. Austin and R. H. H. Pierce, *J. Amer. Chem. Soc.* **55**, 661 (1933).

[2] J. R. Goldsmith, D. L. Graft and O. I. Joensuu, *Geochim. et Cosmochim. Acta* **7**, 221 (1955).

[3] S. T. Yoffe and A. N. Nesmeyanov, *Handbook of Magnesium-Organic Compounds* Vol. II, p. 239. Pergamon Press, London (1956).

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g kg mm cm ml cc cm^3 sec min hr n_D^{25} $[\alpha]_D^{25}$ 25° (without C which is always understood) but m.p., b.p., l. (litre), in. (inch) but in^3.

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SUR LA SYNTHÈSE DU DIBENZO[a,i]PYRÈNE, DU TRIBENZO[a,e,i]PYRÈNE, ET DE NOUVEAUX HOMOLOGUES DU NAPHTO[2,3-a]PYRÈNE

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Institut du Radium, Université de Paris

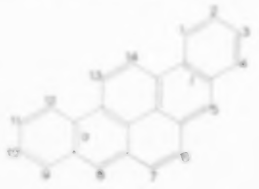
(*Received* 6 *November* 1958)

Résumé—Le dibenzo[a,i]pyrène (I) a été synthétisé à partir du benzo[a]pyrène par condensation avec l'anhydride succinique en position 1, réduction de l'acide cétonique obtenu en acide γ-1-benzo[a]-pyrényl-butyrique, cyclisation en 4-céto-1:2:3:4-tétrahydro-dibenzo[a,i]pyrène, réduction de cette cétone en 1:2:3:4-tétrahydro-dibenzo[a,i]pyrène, et déshydrogénation. D'autre part, la synthèse du tribenzo[a,e,i]pyrène à partir de l'octahydroanthracène symétrique a été réexaminée, et celle de deux nouveaux homologues du naphto[2,3-a]pyrène est décrite.

Abstract—The synthesis of dibenzo[a,i]pyrene is reported, starting from benzo[a]pyrene, obtained by condensation of succinic anhydride in position 1, followed by reduction of the resulting keto acid to γ-1-benzo[a]pyrenylbutyric acid, and cyclisation to 4-keto-1:2:3:4-tetrahydrodibenzo[a,i]pyrene; the latter ketone was reduced to 1:2:3:4-tetrahydrodibenzo[a,i]pyrene, which was then dehydrogenated. Further, the preparation of symmetrical octahydroanthracene has been re-examined, and the synthesis of two new homologues of naphtho[2,3-a]pyrene is described.

Le dibenzo[a,i]pyrène (*I*) est un hydrocarbure important par sa haute activité cancérogène,[1] (c'est en effet le composé le plus puissant connu à l'heure actuelle pour la production des sarcomes), et par le fait qu'il est présent parmi les constituants du goudron de la fumée de tabac.[2] La seule méthode connue jusqu'à présent pour la synthèse de cet hydrocarbure est celle de Scholl et Neumann,[4] améliorée par Clar[5] puis par nous-mêmes,[6] et consistant à réduire la dibenzo[a,i]pyrène-5:8-quinone par la poudre de zinc, cette dernière quinone étant synthétisée à partir du 1:4-dibenzoyl-naphtalène. En raison de l'intérêt que présente l'hydrocarbure (I), nous avons recherché pour ce corps d'autres méthodes de synthèse; dans le présent travail, nous décrirons celle qui utilise, comme matière de départ, le benzo[a]pyrène.

La condensation de l'anhydride succinique sur le benzo[a]pyrène en présence de



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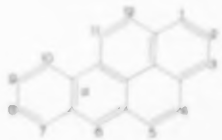

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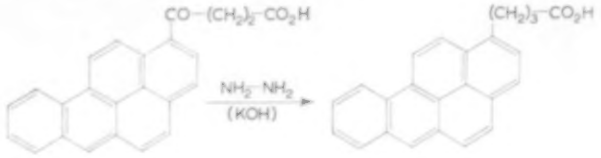
[1] A. Lacassagne, F. Zajdela, N. P. Buu-Hoï et H. Chalvet, *C.R. Acad. Sci., Paris* **244**, 273 (1957); A. Lacassagne, N. P. Buu-Hoï et F. Zajdela, *Ibid.* **246**, 1156 (1958).
[2] B. D. Tilak, M. K. Unni et K. Venkataraman, *Tetrahedron* **3**, 62 (1958).
[3] J. Bonnet et S. Neukomm, *Helv. Chim. Acta* **31**, 1724 (1956).
[4] R. Scholl et H. Neumann, *Ber.* **55**, 118 (1922).
[5] E. Clar, *Ber.* **72**, 1645 (1939).
[6] N. P. Buu-Hoï et D. Lavit, *Rec. Trav. Chim.* **75**, 1194 (1956).

chlorure d'aluminium et en milieu nitrobenzénique, s'effectue principalement en position 1, conduisant à l'acide β-1-benzo[a]pyrénoyl-propionique (III); lorsqu'on emploie le benzène comme solvant, on obtient le même acide, quoique moins commodément. Dans les deux cas, il y a des indices de la formation de traces d'un acide isomère non isolable. Dans la succinoylation, le benzo[a]pyrène se comporte ainsi comme dans l'acétylation[7] et la propionylation,[8] qui avaient déjà été étudiées



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par plusieurs auteurs; la réactivité de la position 1 dans les réactions de Friedel–Crafts est conforme par ailleurs au diagramme des indices de valence libre du benzo[a]pyrène,[9] le sommet 1 ayant l'indice de valence libre le plus élevé après le sommet 6 (*méso*), et l'on sait que les réactions d'acylation selon Friedel–Crafts ne se font pas en général en position *méso*.[10] L'acide β-1-benzo[a]pyrénoyl-propionique peut être réduit en acide γ-1-benzo[a]pyrényl-butyrique (IV), avec d'excellents rendements, par l'hydrate d'hydrazine et la potasse au sein du diéthylèneglycol.[11] La cyclisation du chlorure de

V VI

l'acide (IV), effectuée au moyen du chlorure stannique, conduit au 4-céto-1:2:3:4-tétrahydro-dibenzo[a,i]pyrène (V); cette cétone jaune, soumise à la réduction par l'hydrate d'hydrazine et la potasse, fournit, également avec d'excellents rendements, le 1:2:3:4-tétrahydro-dibenzo[a,i]pyrène (VI). La déshydrogénation de ce dernier hydrocarbure en dibenzo[a,i]pyrène (I) a pu être réalisée au moyen du chloranile en milieu xylènique.

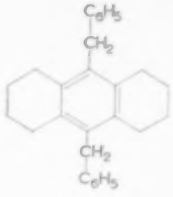
Bien que le rendement en produit final soit faible, et qu'il y ait plus de stades intermédiaires que dans la synthèse de Scholl et Neumann, la méthode d'édification du noyau dibenzo[a,i]pyrénique que nous proposons ici présente l'intérêt que la cétone (V) constitue une voie d'accès possible vers les dibenzo[a,i]pyrènes alkylés en position 4.

Etant donné d'une part le pouvoir cancérogène considérable du dibenzo[a,i]pyrène, et d'autre part, la présence dans le goudron de tabac de plusieurs hydrocarbures aromatiques heptacycliques non encore identifiés, nous nous sommes intéressés à un

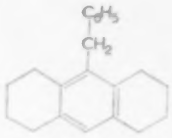
[7] A. Windhaus et S. Rennhak, *Z. physiol. Chem.* **249**, 256 (1937); A. Windhaus et K. Raichle, *Liebigs Ann.* **537**, 157 (1939); L. F. Fieser et E. B. Herschberg, *J. Amer. Chem. Soc.* **61**, 1565 (1939).
[8] N. P. Buu-Hoï, *J. Chem. Soc.* 795 (1946).
[9] N. P. Buu-Hoï, R. et P. Daudel et C. Vroelant, *Bull. Soc. Chim.* **16** [5], 211 (1949).
[10] Par exemple dans le cas de l'anthracène, voir I. G. Farbenindustrie-A.G., brevet français 633.071 (1927).
[11] Huang-Minlon, *J. Amer. Chem. Soc.* **68**, 2487 (1946).

hydrocarbure heptacyclique dérivé de (I), le tribenzo[a,e,i]pyrène (VII). Ce composé a été obtenu par Clar,[12] avec des rendements non précisés, par cyclodéshydrogénation, par le cuivre, du 9:10-dibenzyl-1:2:3:4:5:6:7:8-octahydroanthracène (VIII), ce dernier

VII



VIII



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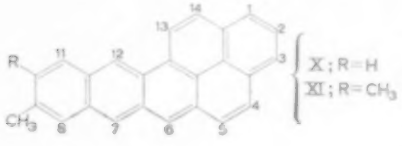
corps étant obtenu par benzylation de l'octahydroanthracène symétrique en présence de chlorure d'aluminium. Dans cette dernière opération, nous avons constaté la formation de 9-benzyl-1:2:3:4:5:6:7:8-octahydroanthracène (IX) à côté du dérivé dibenzylé cherché; la cyclodéshydrogénation de (VIII), réalisée selon la technique de Clar, a bien conduit au tribenzo[a,e,i]pyrène, mais avec des rendements extrêmement faibles (de l'ordre de 0,2%) en hydrocarbure pur, rendements qui diminuent encore lorsque des conditions expérimentales plus énergiques ont été adoptées.

Toujours en vue de l'étude du pouvoir cancérogène d'hydrocarbures condensés dérivés du pyrène, deux nouveaux homologues du naphto[2,3-a]pyrène, le 9-méthylnaphto[2,3-a]pyrène (X) et le 9:10-diméthylnaphto[2,3-a]pyrène (XI) ont été préparés par la réaction d'Elbs respectivement à partir du 1-(2:4-diméthylbenzoyl)pyrène (XII) et du 1-(2:4:5-triméthylbenzoyl)pyrène (XIII); dans la préparation de ces deux



X; R=H
XI; R=CH$_3$

XII; R=H
XIII; R=CH$_3$

dernières cétones (par réaction de Friedel–Crafts des chlorures de *m*-xyloyle et de 2:4:5-triméthylbenzoyle sur le pyrène), nous avons pu isoler de petites quantités des dicétones correspondantes, probablement le 1:6-*bis*(2:4-diméthylbenzoyl)pyrène (XIV) et le 1:6-*bis*(2:4:5-triméthylbenzoyl)pyrène (XV), par analogie avec ce qui a déjà été observé avec le 1:6-dibenzoylpyrène. Il est à noter que la réduction des cétones (XII) et (XIII) par la méthode de Kishner–Wolff est assez difficile, le 1-(2:4-diméthylbenzyl)pyrène et le 1-(2:4:5-triméthylbenzyl)pyrène n'étant obtenus que dans des conditions énergiques.

XIV; R=H
XV; R=CH$_3$

[12] E. Clar, *J. Chem. Soc.* 2168 (1949).

PARTIE EXPÉRIMENTALE (avec Mlle. J. Collard)

Succinoylation du benzo[a]pyrène

(a) *Dans le nitrobenzène.* Le benzo[a]pyrène utilisé est un produit commercial, purifié, F 188–189°; à une solution de 4 g de cet hydrocarbure et 1·6 g d'anhydride succinique dans 100 ml de nitrobenzène anhydre, on ajoute 4·8 g de chlorure d'aluminium finement pulvérisé, en agitant et en refroidissant dans l'eau glacée. On laisse reposer une nuit à temperature ordinaire, décompose par l'acide chlorhydrique dilué, entraîne le nitrobenzène à la vapeur d'eau, et essore le précipité solide formé. Ce dernier est traité par une solution aqueuse bouillante de carbonate de sodium; on filtre à chaud, et acidifie le filtrat refroidi avec ClH; après dessication, le précipité verdâtre ainsi obtenu est traité par le benzène à chaud. La portion peu soluble est recristallisée deux fois dans le chlorobenzène, ce qui conduit à *l'acide β-1-benzo[a]pyrénoyl-propionique* (III), se présentant sous forme de fines aiguilles jaune verdâtre, F 206–207°, donnant avec l'acide sulfurique une halochromie bleu foncé. Rendement: 1 g. Trouvé: C, 82·0; H, 4·4; Calc. pour $C_{24}H_{16}O_3$ (352.37): C, 81·80; H, 4·58%).

La fraction soluble dans le benzène bouillant laisse déposer environ 1 g d'un précipité constitué par le même acide mélangé avec un isomère que nous n'avons pas pu isoler à l'état de pureté. Ce mélange fond vers 196°, mais ne donne pas de dépression du point de fusion par addition d'un échantillon d'acide (III) pur.

(b) *Dans le benzène.* À une suspension de 6 g de benzo[a]pyrène dans 300 ml de benzène anhydre déthiophéné, contenant 2·4 g d'anhydride succinique, on ajoute par petites portions et en remuant, 7 g de Cl_3Al à température ordinaire, puis laisse reposer une nuit (il s'est alors déposé une masse visqueuse rouge violacé). Après décomposition par l'acide chlorhydrique, on traite le produit de la réaction par CO_3Na_2 comme précédemment. Le mélange obtenu est traité par du benzène à froid, qui dissout une petite portion d'acide β-benzoylpropionique (F 107–108°) impur. La portion principale (0·8 g), insoluble dans le benzène froid, est constituée par l'acide (III) mélangé à la même impureté que dans le cas de la succinoylation en milieu nitrobenzénique.

Acide γ-1-benzo[a]pyrényl-butyrique (IV)

Un mélange de 1·2 g de l'acide (III), 1·5 g d'hydrate d'hydrazine à 95%, 1·1 g de potasse caustique et 50 ml de diéthylèneglycol est chauffé deux heures à l'ébullition; après dilution à l'eau et acidification par ClH, on obtient un précipité verdâtre que l'on essore, lave à l'eau, et cristallise deux fois dans le benzène, après dessication. Rendement: 0·6 g de paillettes jaune pâle, F 234–235° (décomp.), donnant une halochromie rouge virant au violet avec SO_4H_2. Trouvé: C, 84·9; H, 5·1; Calc. pour $C_{24}H_{18}O_2$ (338.38): C, 85·18; H, 5·36%).

4-*Céto*-1:2:3:4-*tétrahydro-dibenzo[a,i]pyrène* (V)

On chauffe 3 heures au reflux un mélange de 0·6 g de l'acide précédent, 0·3 g de chlorure de thionyle et 20 ml d'éther anhydre en présence d'une goutte de pyridine; l'acide se dissout peu à peu, en donnant une solution brun rouge. On chasse l'éther et l'excès de $SOCl_2$ sous vide, ajoute 20 ml de benzène anhydre déthiophéné, puis 0·5 g de chlorure stannique (il apparaît aussitôt un précipité rouge violacé), et laisse reposer une nuit. Après décomposition par ClH dilué, on essore le précipité formé, le dissout dans le benzène, lave la solution benzénique à l'eau, sèche sur SO_4Na_2, et chasse le solvant. Le résidu, recristallisé 2 fois dans un mélange d'éthanol et de benzène, conduit à 0·25 g de fines aiguilles jaunes F 223–224°, donnant avec SO_4H_2 une halochromie violette. Trouvé: C, 89·7; H, 5·3; Calc. pour $C_{24}H_{16}O$ (320.37): C, 89.97; H, 5·03%).

1:2:3:4-*Tétrahydro-dibenzo[a,i]pyrène* (VI)

On chauffe 2 heures à l'ébullition un mélange de 0·2 g de la cétone précédente, 0·2 g d'hydrate d'hydrazine, 0·2 g de potasse, et 15 ml de diéthylèneglycol. Après refroidissement, on dilue à l'eau, essore le précipité, le lave à l'eau, le sèche, et le recristallise 2 fois dans le benzène. Rendement: 0·1 g de fines paillettes jaunâtres F 212–213°, donnant avec SO_4H_2 une halochromie rouge virant au violet, et avec l'acide picrique un picrate brun foncé (couleur caractéristique des picrates des 1-alkyl-benzo[a]pyrènes).[7] Trouvé: C, 93·8; H, 6·1; Calc. pour $C_{24}H_{18}$ (306.38): C, 94·08; H, 5·92%).

Dibenzo[a,i]pyrène (I)

On chauffe au reflux pendant 5 heures une solution de 0·35 g de l'hydrocarbure tétrahydrogéné précédent et de 0·7 g de chloranile dans 50 ml de xylène anhydre. Après refroidissement, on ajoute 150 ml d'une solution aqueuse de soude et 150 ml de xylène, et chauffe au reflux pendant 30 minutes pour dissoudre la tétrachlorohydroquinone et le chloranile en excès. La couche xylénique est décantée et lavée à l'eau, séchée sur SO_4Na_2; on chasse le xylène sous vide, et recristallise le résidu plusieurs fois dans le toluène. Rendement: 0·15 g de *dibenzo[a,i]pyrène*, sous forme de paillettes jaune F 280–281° (seule ou en mélange avec un échantillon préparé à partir de la dibenzo[a,i]pyrène-5:8-quinone).

Préparation de l'octahydroanthracène symétrique

Cet hydrocarbure a été préparé par réduction du 1-céto-1:2:3:4:5:6:7:8-octahydroanthracène (58 g) au moyen de l'hydrate d'hydrazine (58 g) et de la potasse (58 g) au sein du diéthylèneglycol (200 ml). Rendement: 42 g de produit E_{14} 163°, F 70–71° à l'état brut. On obtient comme sous-produit de la réaction un peu de *l'azine* du 1-*céto*-1:2:3:4:5:6:7:8-*octahydroanthracène*, cristallisant du benzène en fines aiguilles jaunes F 242°. (Trouvé: N, 6·8; Calc. pour $C_{28}H_{32}N_2$ (396.65): N, 7·08%).

Benzylation de l'octahydroanthracène symétrique

En opérant cette réaction sur 41·5 g d'octahydroanthracène, 58·1 g de chlorure de benzyle et 2·3 g de Cl_3Al dans le tétrachloréthane, on obtient par distillation fractionnée sous vide, 21 g du *dérivé dibenzylé* (VIII), F 189–190°, et quelques grammes de 9-*benzyl*-1:2:3:4:5:6:7:8-*octahydroanthracène* (IX), E_{13} 240–245°, cristallisant de l'éthanol en fines aiguilles incolores, brillants, F 65°. (Trouvé: C, 91·0; H, 8·9; Calc. pour $C_{12}H_{24}$ (276.40): C, 91·25; H, 8·75%).

Tribenzo[a,e,i]pyrène (VII)

Le chauffage à 400–420° d'un mélange de 10 g du dérivé dibenzylé (VIII) avec 1·5 g de poudre de cuivre, effectué d'après la technique de Clar,[12] nous a fourni environ 20 mg de *tribenzo[a,e,i]pyrène* pur, sous forme de paillettes jaune pâle F 333–334°; la littérature indique F 297°. Lorsqu'on élève la température de réaction au-dessus de 420°, les rendements baissent et le produit obtenu est moins pur.

1-(2:4-*Diméthylbenzoyl*)*pyrène* (XII)

A une solution (refroidie dans l'eau glacée) de 15 g de pyrène et 12·5 g de chlorure de 2:4-diméthylbenzoyle dans 50 ml de benzène déthiophéné anhydre, on ajoute 11 g de chlorure d'aluminium par petites portions et en agitant. Après 3 heures à température ordinaire, on décompose par l'acide chlorhydrique dilué; une partie de la cétone précipite sous forme de cristaux jaunes que l'on essore et la couche benzénique filtrée est lavée à la soude aqueuse diluée, puis à l'eau, séchée sur SO_4Na_2, et concentrée, ce qui laisse déposer une nouvelle portion de cette cétone. Après recristallisation dans le benzène, on obtient 10 g du *composé* (XII), sous forme de paillettes jaunâtres, F 134°, donnant avec l'acide sulfurique une halochromie rouge violet. (Trouvé: C, 89·7; H, 5.5; Calc. pour $C_{25}H_{18}O$ (334.39): C, 89·79; H, 5·43%).

Comme sous-produit de la réaction, on obtient 0·1 g de 1:6-*bis*(2:4-*diméthylbenzoyl*)*pyrène* (XIV), cristallisant du benzène sous forme de prismes jaunes, peu solubles, F 264°, donnant avec l'acide sulfurique une halochromie rouge. (Trouvé: C, 87·4; H, 5·6; Calc. pour $C_{34}H_{26}O_2$ (466.6): C, 87·52; H, 5·62%).

9-*Méthylnaphto*[2,3-*a*]*pyrène* (X)

On chauffe à l'ébullition pendant 30 minutes, 6 g de la cétone (XII) dans un tube recourbé, et on distille le produit de la pyrolyse sous vide. Après plusieurs recristallisations dans le benzène, on obtient 0·5 g de magnifiques paillettes jaune d'or, F 254°, donnant avec SO_4H_2 une coloration violette virant au vert. (Trouvé: C, 95·0; H, 5·1; Calc. pour $C_{25}H_{16}$ (316.4): C, 94·90; H, 5·09%).

1-(2:4:5-*Triméthylbenzoyl*)*pyrène* (XIII)

Préparé à partir de 15 g de pyrène, 13 g de chlorure de 2:4:5-triméthylbenzoyle et 11 g de chlorure d'aluminium dans 60 ml de benzène anhydre déthiophéné; rendement: 9 g de la cétone (XIII),

cristallisant du *cyclo*hexane sous forme de prismes jaunâtres, F 145°, donnant avec SO_4H_2 une halochromie rouge violacé. (Trouvé: C, 89·4; H, 5·7; Calc. pour $C_{26}H_{20}O$ (348.42): C, 89·62; H, 5·79%).

Le 1:6-bis(2:4:5-*triméthylbenzoyl*)*pyrène* (XV), obtenu comme sous-produit, avec un rendement de 0·1 g, cristallise du benzène sous forme de prismes jaune pâle, F 309°, donnant avec l'acide sulfurique une halochromie rouge. (Trouvé: C, 87·1; H, 6·2; Calc. pour $C_{36}H_{30}O_2$ (494.60): C, 87·42; H, 6·11%).

9:10-*Diméthylnaphto*[2,3-*a*]*pyrène* (XI)

Obtenu par pyrolyse de la cétone (XIII) dans les mêmes conditions que pour l'homologue inférieur, cet hydrocarbure cristallise du chlorobenzène sous forme de paillettes jaune d'or, F 291°, donnant avec SO_4H_2 une coloration violette virant au vert; rendement: 1 g à partir de 8 g de cétone. (Trouvé: C, 94·3; H, 5·5; Calc. pour $C_{26}H_{18}$ (330.40): C, 94·50; H, 5·49%).

Il est à noter qu'au cours des réactions d'Elbs décrites ici, il n'y a pas eu perte de groupements méthyle, comme cela se produit souvent dans le cas des hydrocarbures dérivés de l'anthracène et du 1:2-benzanthracène.[12]

1-(2:4-*Diméthylbenzyl*)*pyrène*

Une solution de 2·8 g de la cétone (XII) et de 3 g d'hydrate d'hydrazine dans 30 ml de diéthylèneglycol est chauffée à 100° pendant 30 minutes; 3 g de potasse caustique sont ajoutés ensuite, et le mélange est chauffé au reflux pendant 6 heures. Après refroidissement, on verse dans l'eau, essore le précipité formé, et le recristallise plusieurs fois dans l'hexane. Rendement: 1·5 g de fines aiguilles incolores, F 124°. (Trouvé: C, 93·8; H, 6·4; Calc. pour $C_{25}H_{20}$ (320.41): C, 93·71; H, 6·29%).

1-(2:4:5-*Triméthylbenzyl*)*pyrène*

Préparé comme ci-dessus à partir de la cétone (XIII), ce composé cristallise de l'hexane sous forme de fines aiguilles incolores, F 128°. (Trouvé: C, 93·2; H, 6·6; Calc. pour $C_{26}H_{22}$ (334.44): C, 93·37; H, 6·63%).

Remerciements—Ce travail a été effectué grâce à une subvention accordée par le U.S. Department of Health, Education, and Welfare (National Institutes of Health, National Cancer Institute); nos remerciements vont aux autorités de ces organismes.

[12] L. F. Fieser, *Organic Reactions* Vol. I, p. 129. Wiley, New York (1942).

Tetrahedron, 1960, Vol. 8, pp. 7 to 12. Pergamon Press Ltd. Printed in Northern Ireland

LES FACTEURS ÉLECTRONIQUES DANS LA RÉACTION DE FORMYLATION DES HYDROCARBURES AROMATIQUES CONDENSÉS

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Résumé—On montre, par l'étude de la formylation de plusieurs hydrocarbures aromatiques condensés qu'à l'intérieur de chaque classe déterminée d'hydrocarbures, la facilité de formylation est une fonction croissante de l'indice de valence libre sur le sommet qui entre en réaction. Cette règle permet de prévoir, outre la réactivité des hydrocarbures eux-mêmes, également celle des diverses positions à l'intérieur de chacune de ces molécules. On applique ces observations à l'étude du tribenzo[a,c,j]-naphtacène et du phénanthro[2,3-a]pyrène, qui donnent chacun un seul aldéhyde, conformément à la théorie, laquelle indique, comme positions privilégiées, le sommet 17 dans le premier cas, et le sommet 6 dans le second cas.

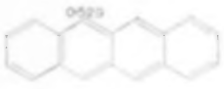
Abstract—A study of the formylation of several condensed aromatic hydrocarbons shows that within each class of such hydrocarbons, the reactivity increases with the free valence index of the position to be substituted. This rule makes it possible to predict not only the behaviour of the hydrocarbons themselves, but also that of the various positions inside each molecule. These considerations are applied to tribenzo[a,c,j]naphtacene and phenanthro[2,3-a]pyrene, each of which gave a single aldehyde, in accordance with the theory, the formylation site predicted being position 17 in the first case, and position 6 in the second.

On sait qu'en raison de la multiplicité des possibilités de substitution présentes dans la molécule des hydrocarbures aromatiques polycycliques, les problèmes concernant la réactivité de ces molécules et ceux ayant trait à la structure de leurs produits de substitution sont en général difficiles à résoudre.[1] Des progrès considérables ont été réalisés à ce point de vue par l'introduction des méthodes de la mécanique quantique, permettant un calcul plus précis de la fonction d'onde représentant les électrons π dans les molécules planes conjugées. En particulier, de nombreux travaux ont établi les relations étroites entre la valeur des indices de valence libre sur les différents sommets substituables chez un hydrocarbure aromatique entièrement constitué de cycles hexagonaux, et la facilité de substitution observée au cours des réactions homolytiques aussi bien qu'hétérolytiques.[2] Réciproquement, les observations expérimentales sur les positions attaquées au cours de ces réactions permettent de vérifier la validité des calculs théoriques. Ces derniers ne sont en général en défaut que dans deux cas: non-planéité de la molécule, comme chez les polyphényles,[3] ou présence de charges électriques, comme chez l'acénaphtylène et le fluoranthène; le cas de ces derniers a déjà été examiné récemment en détail.[4] Nous avons déjà montré à plusieurs reprises qu'en dehors de ces cas exceptionnels, la formylation des hydrocarbures aromatiques

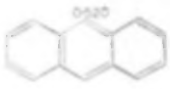
[1] N. P. Buu-Hoï, D. Lavit, P. Jacquignon et O. Chalvet, *Rec. Trav. Chim.* **77**, 462 (1958).
[2] Voir par exemple: N. P. Buu-Hoï, P. et R. Daudel et C. Vroelant, *Bull. Soc. Chim.* **16**, 211 (1949); N. P. Buu-Hoï et R. Daudel, *Ibid.* **16**, 801 (1949).
[3] Voir par exemple: N. P. Buu-Hoï, C. A. Coulson, P. et R. Daudel, M. Martin et A. et B. Pullman, *Rev. Sci.* **85**, 1041 (1947).
[4] N. P. Buu-Hoï et D. Lavit, *Rec. Trav. Chim.* **77**, 724 (1958).

polycycliques au moyen de N-méthylformanilide (ou de diméthylformiamide) en présence d'oxychlorure de phosphore a lieu toujours sur le sommet d'indice de valence libre le plus élevé.[5] Cette réaction offre ainsi un moyen de soumettre les calculs théoriques d'indices de valence libre à une sorte de vérification expérimentale; réciproquement, dans le cas des hydrocarbures très compliqués dans la chimie desquels les déterminations de structure des aldéhydes formés sont impraticables, les indices de valence libre constituent un guide pour l'établissement des formules de constitution.

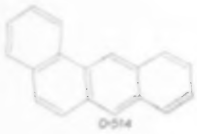
Dans le présent travail, nous examinerons tout d'abord, pour plusieurs séries d'hydrocarbures, la facilité de formylation en fonction des indices de valence libre sur les sommets les plus réactifs. Chez les *hydrocarbures anthracéniques cata-condensés*, l'anthracène lui-même (II) se formyle facilement[6] et le naphtacène (I) est encore plus réactif de ce point de vue;[7] par contre, le benz[a]anthracène (III) est nettement moins réactif que l'anthracène, et pour le dibenz[a,j]anthracène (IV) et le dibenz [a, h] anthracène (V) il n'a pas été obtenu d'aldéhydes. Ces résultats expérimentaux s'expliquent rigoureusement par la décroissance régulière des indices maxima de valence libre comme le montre le tableau suivant:



I

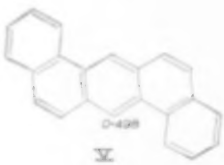


II



III

IV



V

Il semble ainsi que dans cette catégorie d'hydrocarbures, la formylation dans les conditions expérimentales habituelles ne se fasse plus lorsque l'indice maximum de valence libre est égal ou inférieur à 0,510 (il s'agit des indices calculés par les méthodes des orbitales moléculaires).[8] L'importance des répercussions chimiques provoquées par des variations relativement faibles des valeurs de ces indices s'explique par le fait que l'indice de valence libre intervient dans la constante de vitesse d'une réaction supposée bimoléculaire, par l'intermédiaire d'une exponentielle.[9]

Dans la série des *hydrocarbures péri-condensés*, on constate un fait analogue: ainsi, le pyrène (VI) se formyle,[10] tandis que le coronène (VII) dans les mêmes conditions de réaction est tout à fait inerte, les indices maxima de valence libre décroissant dans

[5] N. P. Buu-Hoï et D. Lavit, *Rec. Trav. Chim.* **75**, 1194 (1956); **76**, 200, 321 (1957); N. P. Buu-Hoï et C. T. Long, *Ibid.* **75**, 1121 (1956).
[6] L. F. Fieser et J. Hartwell, *J. Amer. Chem. Soc.* **60**, 2555, 2558 (1938); N. P. Buu-Hoï et N. Hoán, *J. Org. Chem.* **16**, 874 (1951).
[7] N. P. Buu-Hoï et D. Lavit, *Rec. Trav. Chim.* **76**, 674 (1957).
[8] C. A. Coulson et R. Daudel, *Dictionnaire des grandeurs théoriques descriptives des molécules* Vol. II. Mathematical Institute, Oxford, et Centre de chimie théorique de France, Paris (1955).
[9] Voir par exemple: E. C. Kooyman et E. Farenhorst, *Trans. Faraday Soc.* **49**, 58 (1953); R. Daudel et O. Chalvet, *J. Chim. Phys.* 943 (1956).
[10] H. Vollmann, H. Becker, M. Corell, H. Streeck et G. Langbein, *Ann.* **531**, 1 (1937).

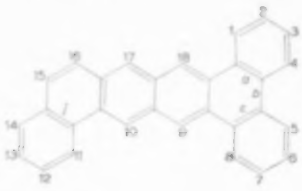
ce même ordre. Il semble donc qu'on puisse admettre que dans le groupe des

VI

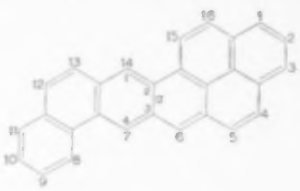
VII

hydrocarbures *péri*-condensés, la formylation ne se fera pas chez les molécules dont les indices maxima de valence libre sont égaux ou inférieurs à 0,449.

Comme application pratique de ces considérations, nous étudions ici le comportement de deux hydrocarbures heptacycliques, le tribenzo[a,c,j]naphtacène (VIII), appartenant à la série *cata*-condensée, et le phénanthro[2,3-a]pyrène (IX), appartenant à la série *peri*-condensée. Le premier de ces hydrocarbures n'avait pas encore été préparé jusqu'à présent; quant au second, il vient d'être signalé par Boggiano et

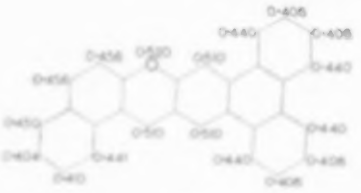


VIII

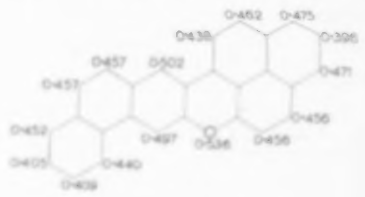


IX

Clar,[11] qui l'ont préparé par une méthode légèrement différente de la nôtre. Les diagrammes moléculaires A et B de ces deux hydrocarbures ont été calculés par la *méthode des abaques, les indices de liaison et de valence libre étant homogènes à* ceux obtenus par la méthode des combinaisons linéaires d'orbitales atomiques; l'approximation ainsi obtenue est suffisante pour l'usage que nous en faisons ici.



A



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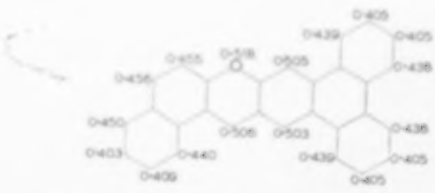
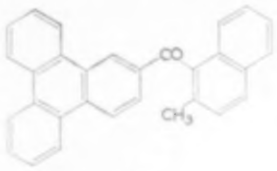


C

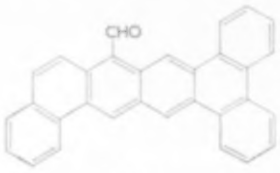
[11] B. Boggiano et E. Clar, *J. Chem. Soc.* 2681 (1957).

D'ailleurs, les différences avec les chiffres calculés plus rigoureusement au moyen de la machine électronique du National Physical Laboratory à Teddington* sont faibles, comme le montre pour le tribenzo[a,c,j]naphtacène[12] la comparaison des diagrammes moléculaires A et C, ce dernier étant calculé par la méthode des combinaisons linéaires d'orbitales atomiques.

Le tribenzo[a,c,j]naphtacène a été obtenu avec des rendements assez substantiels par pyrolyse du 2-(2-méthyl-1-naphtoyl) triphénylène (X); cette dernière cétone a été préparée par une réaction de Friedel–Crafts entre le triphénylène et le chlorure de



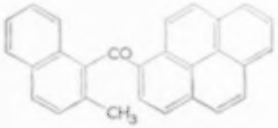
X



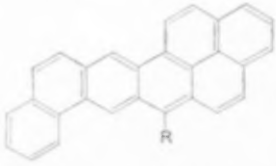
XI

2-méthyl-1-naphtoyle, cette opération conduisant à une cétone unique, comme dans le cas des réactions similaires déjà pratiquées sur le triphénylène.[13] L'hydrocarbure jaune (VIII) ainsi obtenu est assez peu réactif vis-à-vis de la N-méthylformanilide en présence d'oxychlorure de phosphore; un aldéhyde a toutefois été isolé, auquel nous assignons la structure du 17-formyl-tribenzo[a,c,j]naphtacène(XI), sur la base du diagramme moléculaire qui assigne à la position 17 l'indice le plus élevé.

Quant au phénanthro[2,3-a]pyrène, nous l'avons préparé par pyrolyse du 3-(2-méthyl-1-naphtoyl) pyrène (XII), cétone que nous avons obtenue avec d'excellents rendements, par une réaction de Friedel-Crafts entre le pyrène et le chlorure de 2-méthyl-1-naphtoyle; Boggiano et Clar ont préparé cette cétone avec des rendements inférieurs et à l'état moins pur, en condensant le chlorure de l'acide pyrène-3-carboxylique avec le β-méthylnaphtalène. Il est à noter que la pyrolyse de (XII), qui, normalement, devrait conduire à un hydrocarbure *cis*-bisangulaire, s'est faite avec transposition moléculaire, de façon à ne donner que l'hydrocarbure isomère de structure *trans*-bisangulaire.[14] La formylation de cet hydrocarbure a fourni, avec de bons rendements, un seul aldéhyde, auquel nous assignons la structure du 6-formulphénanthro[2,3-a]pyrène (XIII); en effet, d'après les calculs théoriques, c'est le



XII



XIII; R = −CHO
XIV; R = −CH3

sommet 6 auquel correspond l'indice de loin le plus élevé. La réduction de l'aldéhyde (XIII) par l'hydrate d'hydrazine et la potasse conduit, avec d'excellents rendements, au 6-méthyl-phénanthro[2,3-a]pyrène (XIV).

* Nous tenons à remercier particulièrement le Docteur Wilkinson qui a bien voulu assurer la direction des calculs numériques.

[12] O. Chalvet et C. Moser, Résultats inédits.
[13] N. P. Buu-Hoï et P. Jacquignon, *J. Chem. Soc.* 941 (1953).
[14] J. W. Cook, *J. Chem. Soc.* 487 (1931); 1472 (1932).

En résumé, comme il a été montré[1] que l'on pouvait utiliser les prédictions fournies par la théorie en vue de la recherche des sommets réactifs par formylation, nous avons étendu cette technique au cas d'hydrocarbures aromatiques heptacycliques, l'identification expérimentale des produits obtenus étant en cours.

PARTIE EXPÉRIMENTALE

2-(2-Méthyl-1-naphtoyl)triphénylène (X). A une solution de 11 g de triphénylène et de 13 g de chlorure de 2-méthyl-1-naphtoyle dans 350 ml de sulfure de carbone anhydre, on ajoute par petites portions et en remuant, 11 g de chlorure d'aluminium en poudre fine; on laisse la nuit à température ordinaire, chauffe ensuite 2 heures au reflux, et décompose ensuite par le glace et l'acide chlorhydrique. On reprend le produit de la réaction par du chloroforme, lave à la soude diluée, puis à l'eau, séche sur SO_4Na_2 et chasse les solvants. Le résidu fournit après cristallisation dans un mélange de benzène et d'éthanol, 5·5 g de fines aiguilles presque incolores, F 224°, donnant avec l'acide sulfurique une halochromie rouge. (Trouvé: C, 90·8; H, 5·3; Calc. pour $C_{30}H_{20}O$ (396.46): C, 90·88; H, 5·09%).

Tribenzo[a,c,j]naphtacène (VIII). On chauffe 5·4 g de la cétone précédente à l'ébullition dans un tube recourbé, jusqu'à cessation de dégagement de vapeur d'eau (20 min); à la distillation sous vide, on recueille, après une tête jaune clair (constituée par la cétone récupérée), une fraction jaune vif, que l'on recristallise dans le xylène. Rendement: 1·5 g de fines aiguilles jaunes, F 280°, donnant avec SO_4H_2 une halochromie verte. (Trouvé: C, 95·0; H, 4·8; Calc. pour $C_{30}H_{18}$ (378.44): C, 95·21; H, 4·79%).

17-Formyl-tribenzo[a,c,j]naphtacène (XI). Un mélange de 1·2 g de l'hydrocarbure (VIII), 0·7 g de N-méthylformanilide, 0·7 g d'oxychlorure de phosphore et 20 ml d'*o*-dichlorobenzène anhydre est chauffe 5 heures au bain-marie bouillant; on ajoute ensuite une solution aqueuse concentrée d'acétate de sodium, et chauffe au reflux pendant 30 min. On entraîne l'*o*-dichlorobenzène à la vapeur d'eau, essore le résidu, et le dessèche. Par cristallisation fractionnée dans le chlorobenzène, on isole 0·8 g d'hydrocarbure récupéré, puis 0·3 g d'un aldéhyde constituant de fines aiguilles jaune orangé, F 318°, donnant avec SO_4H_2 une halochromie violet foncé. (Trouvé: C, 91·3; H, 4·5; Calc. pour $C_{31}H_{18}O$ (406.49): C, 91·60; H, 4·5%).

3-(2-Méthyl-1-naphtoyl)pyrène (XII). A une solution de 13 g de pyrène et 13 g de chlorure de 2-méthyl-1-naphtoyle dans 130 ml de benzène anhydre refroidie dans un bain de glace, on ajoute par petites portions et en remuant, 9·5 g de chlorure d'aluminium. Après 3 heures de repos à temperature ordinaire, on décompose par la glace et l'acide chlorhydrique, essore le précipité formé, le lave avec un peu de benzène froid, le sèche, et le recristallise dans un mélange d'éthanol et de benzène. Rendement: 21 g de cristaux jaunes, F 198°, donnant avec l'acide sulfurique une halochromie rouge violacé; Boggiano et Clar indiquent F 194–195°.

Phénanthro[2,3-a]pyrène (IX). On chauffe 10·5 g (en deux fois) de la cétone précédente à l'ébulli tion dans un tube recourbé, jusqu'à cessation du dégagement d'eau (30 min); le produit de la réaction d'Elbs est distillé sous vide, et aprés des têtes jaune clair constituées par la cétone récupérée, on recueille un produit jaune orangé (5·6 g), qu'on triture avec du xylène chaud, essore et recristallise dans le chlorobenzène. Rendement: 2·3 g de belles paillettes jaune orangé, F 329–330°, donnant avec l'acide sulfurique une halochromie violette virant au vert sombre.

6-Formyl-phénanthro[2,3-a]pyrène (XIII). On chauffe 6 heures au bain-marie bouillant un mélange de 1·9 g de l'hydrocarbure (IX), 1·1 g de N-méthylformanilide, 1·2 g d'oxychlorure de phosphore et 25 ml d'*o*-dichlorobenzène. On traite ensuite comme pour l'hydrocarbure (VIII). Rendement: 1·4 g d'aldéhyde (XIII), cristallisant du chlorobenzène en aiguilles brun rouge, F 293°, donnant avec l'acide sulfurique une halochromie violette. (Trouvé: C, 91·5; H, 4·2; Calc. pour $C_{29}H_{16}O$ (380.42): C, 91·57; H, 4·21%).

6-Méthyl-phénanthro[2,3-a]pyrène (XIV). Une suspension de 1·3 g de l'aldéhyde précédent dans 250 ml de diéthylèneglycol est chauffée avec 1.5 g d'hydrate d'hydrazine à 95° jusqu'à dissolution complète; on ajoute 1·3 g de potasse caustique et chauffe au reflux pendant 30 minutes. Après refroidissement, on dilue à l'eau, essore le précipité obtenu, le lave à l'eau, le sèche, et le recristallise dans le chlorobenzène (avec du noir animal). Rendement: 1 g de fines aiguilles jaune orangé, F 308°, donnant avec l'acide sulfurique une halochromie violacée virant au vert foncé. (Trouvé: C, 94·8; H, 5·0; Calc. pour $C_{29}H_{18}$ (366.43): C, 95·05; H, 4·95%).

Essai de formylation du coronène. Un mélange de 2 g de coronène en poudre fine, de 1·3 g de

N-méthylformanilide et de 1·4 g d'oxychlorure de phosphore dans 50 ml d'*o*-dichlorobenzène est chauffé pendant 6 heures au bain-marie bouillant; après refroidissement, on essore le précipité de coronène non-dissout, et le filtrat est traité par une solution aqueuse concentrée et bouillante d'acétate de sodium. Après entraînement à la vapeur d'eau, il ne reste qu'un très faible résidu, qui est constitué par du coronène; quant à la fraction insoluble qui avait été essorée, elle donne après recristallisation dans l'*o*-dichlorobenzène, 1·9 g de cristaux jaunâtres de *coronène*, F 438° (littérature[13]): F 438–440°). La recherche de traces de formylcoronène dans les eaux-mères de cristallisation des deux fractions de coronène par une halochromie éventuelle avec l'acide sulfurique a été négative.

Essai de formylation du dibenz[a,j]anthracène (IV). Cet hydrocarbure (F 196°) a été préparé à l'état pur par cristallisation fractionnée dans le benzène ou dans le *cyclo*hexane, d'un produit commercial contenant, comme impureté, environ 20% de dibenz [*a*, *h*] anthracène, qui cristallise en premier. Une tentative de formylation de l'hydrocarbure (IV), exécutée dans les mêmes conditions que ci-dessus, n'a pas non plus donné de dérivé formylé, et l'hydrocarbure mis en jeu a été entièrement récupéré.

Les hydrocarbures décrits dans ce travail sont en cours d'étude biologique dans notre Institut, au point de vue de leur activité cancérogène éventuelle.

Remerciements—Ce travail a été effectué grâce à une subvention accordée par le U.S. Department of Health, Education, and Welfare (National Institutes of Health, National Cancer Institute); nos remerciements vont aux autorités de ces organismes.

[13] M. S. Newman, *J. Amer. Chem. Soc.* **62**, 1683 (1940).

Tetrahedron, 1960, Vol. 8, pp. 13 to 22. Pergamon Press Ltd. Printed in Northern Ireland

BOND LENGTHS IN BENZENE DERIVATIVES

HYBRIDIZATION OR RESONANCE

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Abstract—The measured bond lengths in nitrobenzene and in other simple benzene derivatives indicate that there is little or no resonance involving excited structures. The bond length variations can however be explained by differences in hybridization of the carbon σ orbitals.

INTRODUCTION

The shortening of C–C bond lengths (in comparison with the usual single bond distance) in conjugated or hyperconjugated molecules, such as butadiene or propylene, is generally attributed to the effects of π-electron resonance. Recently Dewar and Schmeising[1] have questioned the interpretation of the evidence for the existence of appreciable π-electron resonance in the ground states of conjugated or hyperconjugated molecules, and have concluded that all observed effects are explainable as a result of differences in hybridization of carbon σ orbitals, resonance effects being negligible. They suggest that resonance is important only in those molecules, such as benzene, where more than one classical (unexcited) structure can be written, but that even in these cases the effects of π-electron resonance are much smaller than is usually believed.

Mulliken[2] has further examined this problem and has concluded that, while Dewar and Schmeising are partly right in suggesting that the lengths of conjugated and hyperconjugated C–C bonds are determined, to a greater extent than is usually supposed, by the states of hybridization of the carbon bond orbitals rather than by π-electron resonance, there seems to be no justification for the assumption that the π-delocalization shortenings are negligible. He has analysed the C–C bond length shortenings in several conjugated and hyperconjugated molecules, and has attributed 40 per cent of the observed shortenings to π-electron resonance, and 60 per cent to hybridization differences.

We have recently completed a detailed X-ray analysis of the crystal and molecular structure of nitrobenzene at $-30°$,[3] and the measured bond lengths and valency angles provide some additional information on the problem of the relative importance of resonance and of hybridization differences. One difficulty in estimating the value of the evidence provided by the measured dimensions of the nitrobenzene molecule is that the accuracy of the results obtained by X-ray diffraction of crystals is not nearly as good as that given by spectroscopic methods, although of course the X-ray method has the advantage of being able to deal with more complex molecules. The estimated standard deviations of the carbon–carbon bond lengths in nitrobenzene,

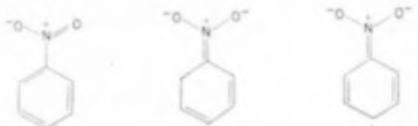
* National Research Council Postdoctorate Fellow.

[1] M. J. S. Dewar and A. N. Schmeising, *Tetrahedron* **5**, 166 (1959).
[2] R. S. Mulliken, *Tetrahedron* **6**, 68 (1959).
[3] J. Trotter, *Acta Cryst.* **12**, 884 (1959).

for example, are 0·014 Å, while the spectroscopic method for simpler molecules gives an accuracy of the order of 0·001 Å. We did not therefore feel justified in basing our conclusions only on the results of the investigation of the nitrobenzene structure, and we also examined the results of X-ray investigations of other mono-substituted benzenes reported in the literature.

NITROBENZENE

Resonance theory predicts that in nitrobenzene (I), as in other simple benzene derivatives, contributions to the ground state of the molecule from ionic (excited) structures such as II and III decrease the length of the C–N bond, in comparison with



I II III

the corresponding distance in a non-conjugated molecule, and in addition lead to variations of the carbon–carbon bond lengths from the distances in benzene, such that bonds 1–2 and 1–6 are the longest and 2–3 and 5–6 the shortest in the aromatic ring. Calculations by molecular orbital methods show that the variations to be expected in carbon–carbon bond lengths are quite small; for nitrobenzene, for example, a simple calculation[4] shows that the predicted lengths of the bonds 1–2, 2–3, 3–4 are 1·399 1·392, 1·394 Å respectively. The predicted shortening of the C–N bond is much greater than these rather small variations, although it is difficult to make an exact

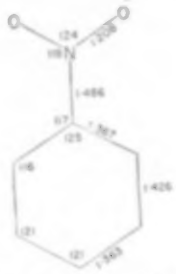


FIG. 1. Bond lengths (Å) and valency angles (degrees) in nitrobenzene.

estimate because of uncertainties in the bond order-bond length correlation curve in the range of bond orders involved.[4]

The X-ray analysis of the crystal and molecular structure of nitrobenzene at −30° revealed that the molecule was completely planar with symmetry *mm*2 (we did not feel at the outset of the analysis that this would necessarily be so, as the *p*-dinitrobenzene molecule, for example, has been shown to be slightly non-planar,[5] at least in the solid state); the bond lengths and valency angles in the nitrobenzene molecule are shown in Fig. 1. The values of the bond distances indicate, firstly that the variations in the lengths of carbon–carbon bonds are much larger than predicted by resonance

[4] J. Trotter, *Canad. J. Chem.* **37**, 905 (1959).
[5] S. C. Abrahams, *Acta Cryst.* **3**, 194 (1950).

theory, and in addition in the wrong direction, bonds 2–3 and 5–6 being significantly longer than the other aromatic bonds; and secondly that the C–N bond is not shortened in comparison with the corresponding bond in a non-conjugated molecule and indeed it is a little longer than the value usually quoted for the C–N single bond distance (1·475 Å). These points will be discussed in turn.

C–C bond lengths

The estimated standard deviations of the measured carbon–carbon bond lengths in nitrobenzene are 0·014 Å, so that bond 1–2 does not differ significantly in length from bond 3–4, but bond 2–3 is very significantly longer (0·06 Å) than the other two chemically-independent carbon-carbon bonds in the aromatic ring. These bond length variations are in the opposite direction to those predicted by resonance theory, and suggest that changes in the hybridization of the aromatic carbon atoms from those in benzene result in changes in the carbon–carbon bond lengths which are much larger than any variations due to π-electron resonance. We have not carried out any elaborate calculations, but some quite simple considerations indicate that the bond length variations can be explained on the basis of changes in carbon atom hybridizations. It would be expected that an increase in the valency angle in the aromatic ring at one of the carbon atoms would shorten the aromatic bonds involving that atom, since there is an increase in the *s* character of the hybrid orbitals, and conversely a decrease in valency angle would increase the bond lengths. Taking the carbon–carbon bond lengths in benzene as 1·392 Å (the value determined by X-ray diffraction methods), the covalent radius of a carbon atom in benzene is 0·696 Å. Utilizing the measured bond lengths in nitrobenzene, and taking $r_3 = r_4$ since the angles at these atoms are equal, we obtain for the effective covalent radii of the carbon atoms in the aromatic bonds:

$$r_1 = 0{\cdot}623 \text{ Å}$$

$$r_2 = 0{\cdot}744$$

$$r_3 = 0{\cdot}682$$

$$r_4 = 0{\cdot}682$$

An approximately linear correlation may then be established between valency angle and effective covalent radius (Fig. 2), which of course gives an adequate account of the dimensions of the aromatic ring in the nitrobenzene molecule (Table 1). This procedure is approximately equivalent to using the expressions given by Coulson[6] for the hybridization ratio, λ, in a hybrid orbital.

The validity of this correlation may be judged by using the method for predicting bond length variations in other molecules. We applied Fig. 2 to the calculation of the type of bond length variation to be expected in nitromesitylene. The valency angles in the aromatic ring (Fig. 3), determined by X-ray analysis of the crystalline material,[7] differ by greater amounts from the 120° in benzene than do the angles in the nitrobenzene molecule. These larger deviations are probably the result of steric effects which twist the nitro group about the C–N bond 66° out of the aromatic plane. Using

[6] C. A. Coulson, *V. Henri Memorial Volume* p. 15. Desoer, Liége (1948).
[7] J. Trotter, *Acta Cryst.* **12**, 605 (1959).

TABLE 1. MEASURED AND CALCULATED BOND LENGTHS (Å)

Molecule	Bond	Measured length	Length calculated from Fig. 2.
Nitrobenzene	1–2	1·37	1·38
	2–3	1·43	1·43
	3–4	1·36	1·37
Nitromesitylene	1–2	1·37	1·37
	2–3	1·41	1·43
	3–4	1·37	1·38

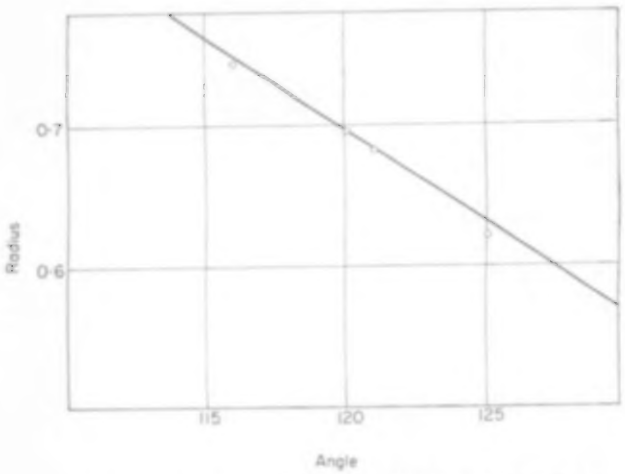


FIG. 2. Effective covalent radius as a function of valency angle.

FIG. 3. Bond lengths (Å) and valency angles (degrees) in nitromesitylene.

the measured valency angles, the effective atomic radii of the aromatic carbon atoms, determined from Fig. 2, are:

$$r_1 = 0{\cdot}564 \text{ Å}$$

$$r_2 = 0{\cdot}803$$

$$r_3 = 0{\cdot}630$$

$$r_4 = 0{\cdot}750$$

The corresponding values of the aromatic carbon–carbon bond lengths are compared in Table 1 with the measured values, and the agreement is reasonably good considering the accuracy of the measured values and the rather approximate method for estimating the calculated values.

It would appear then that it is reasonable to ascribe the aromatic bond length variations in nitrobenzene and nitromesitylene to changes in hybridization of the carbon σ orbitals from those in benzene, and that the rather approximate method suggested for allowing for these differences in hybridization gives quite good agreement with the observed effects. We would not expect Fig. 2 to be accurately applicable to other benzene derivatives, since the bond lengths used in deriving it have been measured with limited accuracy, but some correlation of this type may be useful for other molecules.

Although the C–C bond length variations can be correlated with the changes in hybridization, it is not immediately apparent why such differences in valency angle should occur. One possible explanation is the steric effect of the substituent nitro group on the *ortho* hydrogen atoms in nitrobenzene. That this is a reasonable explanation is supported by the rather larger differences in valency angles in nitromesitylene, where the methyl groups produce considerable steric strain in the molecule and indeed cause significant deviations from coplanarity. It is possible also of course that intermolecular forces in the crystal have a small effect.

Although we can ascribe all the variations in the carbon–carbon bond lengths to hybridization differences, this does not in itself necessarily imply that π-electron resonance (apart from that in benzene and the nitro group separately) is negligible, since the bond length variations predicted by resonance theory would probably be too small to be observed accurately by X-ray diffraction methods, even if they could be separated from the hybridization effects. The C–N bond distance, for which resonance theory predicts a considerable shortening, ought to yield more information about the relative magnitudes of resonance and hybridization in nitrobenzene.

C–N bond length

The derivation of C–N bond lengths in aromatic nitro compounds by molecular orbital methods is complicated by uncertainties in the bond order bond length correlation curve in the range of bond orders involved.[4] Two different and equally plausible correlation curves give values of 1·39 Å and 1·43 Å for the calculated carbon–nitrogen bond distance in nitrobenzene.

Calculations by the molecular orbital method[4] show that resonance increases the bond order of the C_2–C_3 bond in nitrobenzene from 0·667 to 0·675, but the order of the C–N bond from 0 to 0·322; apart then from possible differences in the forms of the C–C and C–N order–length correlation curves in the regions of bond order involved,

we should expect the shortening of the C–N bond to be about 40 times that of the C_2–C_3 bond, that is about 0·04 Å.

The value usually quoted for the C–N bond length in nitromethane is 1·47 Å, although a value of 1·49 Å has recently been given.[8] For aromatic nitro compounds values as low as 1·35 Å have been reported for picryl iodide[9] and 1:5-dinitronaphthalene,[10] although for the latter molecule a recent redetermination of the crystal structure[11] has shown that the C–N distance is actually 1·486 Å—identical with the corresponding distance in nitrobenzene. For *m*-dinitrobenzene values as far apart as 1·39 Å and 1·54 Å have been reported in different investigations,[12,13] while the C–N bond length in *p*-dinitrobenzene[5] has been measured as 1·48 Å.

It is probably more useful to compare the C–N bond length in nitrobenzene (1·486 Å) with the lengths in aromatic nitro compounds in which any resonance interaction between the nitro group and the aromatic rings is reduced by some means. In nitromesitylene the steric effects of neighbouring carbon and hydrogen atoms prevent the nitro group from being coplanar with the plane of the aromatic rings, and X-ray analysis[7] has shown that the NO_2 group is rotated about the C–N bond 66° out of the aromatic plane, the C–N distance being 1·48 Å; the twist of 66° implies that resonance interaction across the C–N bond is only about 0·17 ($\cos^2 66°$) of that in a coplanar structure. In 9-nitroanthracene[14] similar steric effects twist the nitro group 85° out of the anthracene plane, so that the C–N bond length in this molecule (1·48 Å) may be taken as the distance in a non-conjugated nitro compound with a trigonal carbon atom. The measured carbon–nitrogen bond distance in nitrobenzene suggests that, if there is any shortening as the result of resonance interaction, it is more or less balanced by a lengthening due to differences in hybridization of the carbon and nitrogen atoms in nitrobenzene and in 9-nitroanthracene. However the exocyclic valency angles in nitrobenzene are identical with those in 9-nitroanthracene, so that the hybridization effects should be the same for the C–N bonds in both molecules. The apparent reasonable conclusion is that any resonance interaction across the C–N bond in nitrobenzene is insufficient to cause any measurable shortening of the bond distance.

We would prefer not to be too dogmatic about this conclusion, since the accuracy of the X-ray results does not definitely exclude, for any one molecule, the possibility of the non-observance of a shortening of the C–N bond being due to experimental error. Nevertheless in none of the nitro compounds we have studied is the C–N distance (these are summarized in Table 2) significantly shorter than 1·48 Å. Indeed only for 9:10-dinitroanthracene[15] is the difference as great as 0·03 Å, and the accuracy of that particular analysis is such that this is still only possibly significantly less than 1·48 Å.

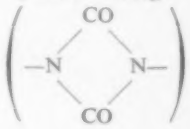
It appears then that in nitrobenzene the measured lengths of the C–C and C–N bonds indicate no variations and shortenings such as are predicted by resonance theory.

[8] *Tables of Interatomic Distances and Configurations in Molecules and Ions.* Chemical Society Special Publication No. 11, London (1958).
[9] G. Huse and H. M. Powell, *J. Chem. Soc.* 1398 (1940).
[10] N. G. Sevastyanov, G. S. Zhdanov and M. M. Umansky, *J. Phys. Chem. Russ.* **22**, 1153 (1948).
[11] J. Trotter, *Acta Cryst.* In press.
[12] N. W. Gregory and E. N. Lassettre, *J. Amer. Chem. Soc.* **69**, 102 (1947).
[13] E. M. Archer, *Proc. Roy. Soc.* A **188**, 51 (1946).
[14] J. Trotter, *Acta Cryst.* **12**, 237 (1959).
[15] J. Trotter, *Acta Cryst.* **12**, 232 (1959).

TABLE 2. C–N BOND LENGTHS

Molecule	Nitro group twist	C–N distance
Nitrobenzene	0°	1·49 Å
1:5-Dinitronaphthalene	49	1·49
9:10-Dinitroanthracene	64	1·45
Nitromesitylene	66	1·48
9-Nitroanthracene	85	1·48

TABLE 3. BOND LENGTHS IN BENZENE DERIVATIVES (Å)

Molecule	Aromatic bonds			Exocyclic bonds		
	1–2	2–3	3–4	C–C	C–N	
Benzene[16]	1·39	1·39	1·39	—	—	
Dibenzyl[17]	1·37	1·39	1·37	1·52	—	
Nitrobenzene[3]	1·37	1·43	1·36	—	1·49	($-NO_2$)
Nitromesitylene[7]	1·37	1·41	1·37	—	1·48	($-NO_2$)
Benzoic acid[18]	1·39	1·41	1·36	1·48	—	
Acetanilide[19]	1·38	1·40	1·39	—	1·43	($-NH\cdot COCH_3$)
Phenyl isocyanate dimer[20]	1·35	1·39	1·37	—	1·41	
KH Dibenzoate[21]	1·37	1·40	1·37	1·53	—	
Ephedrine hydrochloride[22]	1·37	1·44	1·36	1·56	—	
p-Toluidine hydrochloride[23]	1·38	1·42	1·39	—	1·45	($-NH_3$)
Mean	$1·37_2$	$1·41_0$	$1·37_1$			

OTHER BENZENE DERIVATIVES

As we pointed out in the introduction we do not feel justified in basing our conclusions only on the analysis of the crystal structures of nitrobenzene and nitromesitylene, and we have collected in Table 3 the measured bond lengths in most of the monosubstituted benzene derivatives which have been examined reasonably accurately by the X-ray method (nitromesitylene and *p*-toluidine hydrochloride have methyl substituents in addition to the functional group). These data were taken chiefly from *Tables of Interatomic Distances*.[8] In a few of the investigations reported in the literature the measured aromatic bond lengths do not differ significantly from

[16] E. G. Cox, D. W. J. Cruickshank and J. A. S. Smith, *Proc. Roy. Soc.* A **247**, 1 (1958).
[17] D. W. J. Cruickshank, *Acta Cryst.* **2**, 65 (1949).
[18] G. A. Sim, J. M. Robertson and T. H. Goodwin, *Acta Cryst.* **8**, 157 (1955).
[19] C. J. Brown and D. E. C. Corbridge, *Acta Cryst.* **7**, 711 (1954).
[20] C. J. Brown, *J. Chem. Soc.* 2931 (1955).
[21] J. M. Skinner, G. Stewart and J. C. Speakman, *J. Chem. Soc.* 180 (1954).
[22] D. C. Phillips, *Acta Cryst.* **7**, 159 (1954).
[23] G. von Eller, *Bull. Soc. Fr. Min. Crist.* **78**, 257 (1955).

the mean value, and we have not listed any of these; and in a few cases bond length variations are more or less haphazard. In all the molecules listed in Table 3 (except perhaps acetanilide) we are justified in assuming that the symmetry of the aromatic ring does not differ significantly from *mm*2.

In all of these more accurate structure investigations the variations of the aromatic bond lengths are much larger than and in the opposite direction to those predicted by

TABLE 4. BOND ANGLES IN BENZENE DERIVATIVES (DEGREES)

Molecule	Angles			
	1	2	3	4
Benzene	120	120	120	120
Dibenzyl	—	—	—	—
Nitrobenzene	125	116	121	121
Nitromesitylene	130	112	125	116
Benzoic acid	119	119	122	118
Acetanilide	121	119	120	120
Phenyl isocyanate dimer	120	120	121	118
KH Dibenzoate	—	—	—	—
Ephedrine hydrochloride	123	118	120	121
p-Toluidine hydrochloride	121	119	121	119
Mean	122·$_7$	117·$_6$	121·$_4$	119·$_8$

resonance theory, the mean values of the lengths of bonds 1–2, 2–3 and 3–4 being $1{\cdot}37_2$, $1{\cdot}41_0$, $1{\cdot}37_1$ Å respectively. The valency angles in the aromatic rings in all the molecules in Table 3 are listed in Table 4. The mean values were used to obtain from Fig. 2 the mean values of the effective covalent radii of the aromatic carbon atoms:

$$r_1 = 0{\cdot}660 \text{ Å}$$

$$r_2 = 0{\cdot}728$$

$$r_3 = 0{\cdot}677$$

$$r_4 = 0{\cdot}710$$

The corresponding calculated values of the aromatic bond lengths are 1–2 = 1·388 Å, 2–3 = 1·405 Å, 3–4 = 1·387 Å, in reasonable agreement with the measured values. The correlation in Fig. 2 has of course been derived from the nitrobenzene results only, and a slightly different straight line would give better overall agreement between measured and calculated bond lengths for all the molecules.

It must be emphasized that the data in Tables 3 and 4 are subject to appreciable and varying uncertainties. The standard deviations of the individual bond lengths for the first seven molecules listed are of the order of 0·01 Å, so that only bond length differences greater than about 0·03–0·04 Å are really significant for any individual molecule. For the last three molecules the possible errors are even greater.

Although for any individual molecule then it would be unwise to draw any definite conclusions from the measured bond length variations (for benzoic acid for example

Goodwin[24] points out that the bond length variations are definitely in the opposite direction to those predicted by resonance theory, but that an accurate three-dimensional analysis may perhaps alter this conclusion) the accumulation of evidence from all the molecules listed supports overwhelmingly the view that no variations in the aromatic carbon–carbon bonds due to resonance are observed, but that hydridization differences result in significant variations of the bond lengths.

No detailed discussion of the exocyclic bond lengths will be attempted (except for that given above for C–N bonds in nitro compounds) since the substituent groups vary widely.

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It is instructive though to compare the C–N distances in nitro compounds, where any resonance would be theoretically of the weakest type (dative and sacrificial), with the corresponding bond lengths in molecules such as aniline, where the resonance is dative isovalent and is therefore expected to be much stronger than in nitrobenzene. Examination of Table 3 indicates that the C–N distances in molecules with dative isovalent conjugation are about 1·43 Å, considerably shorter than the corresponding distances in nitro compounds. Unfortunately there is not a whole series of molecules of this type where we would expect differences in the resonance interaction (as for the nitro compounds listed in Table 2), but the measured distances available do suggest that the C–N bonds are shortened by resonance. In *p*-nitroaniline (which is not included in Table 3, since there are two functional groups) the bond lengths are $C–NO_2 = 1·41$ Å, $C–NH_2 = 1·37$ Å.[25] Further accurate measurements of the bond lengths in amines are required before more definite conclusions can be drawn.

FURTHER CONSIDERATIONS

The aromatic carbon–carbon bond lengths in nitrobenzene and other simple benzene derivatives indicate then that no variations due to resonance involving ionic (excited) structures are observed, but that differences in the hybridization of the carbon σ orbitals from those in benzene produce considerable variations in the C–C bond lengths. In all the aromatic nitro compounds which we have investigated by the X-ray method, no shortenings in the C–N distances in comparison with non-conjugated molecules, such as are predicted by resonance theory, have been observed.

Both these lines of evidence suggest that in the ground state resonance involving excited structures is negligible—in agreement with the conclusion reached by Dewar and Schmeising.[1] The ground state of the nitrobenzene molecule can be represented as a resonance hybrid of the structures IV–VII. The measured bond lengths also

IV V VI VII

indicate that calculated bond lengths for this type of molecule, derived by molecular orbital methods, are more or less worthless, but that an approximate allowance for hybridization changes gives good agreement with measured values.

[24] T. H. Goodwin, *J. Chem. Soc.* 4451 (1955).
[25] J. Donohue and K. N. Trueblood, *Acta Cryst.* **9**, 960 (1956).

It is possible of course that there are small contributions from ionic structures, which are insufficient to produce measurable shortenings of the C–N bond distances, but could affect properties such as dipole moment.

As Dewar and Schmeising[1] point out, several other properties are commonly quoted as evidence for π-delocalization in conjugated and hyperconjugated molecules. The higher dipole moment of nitrobenzene (3·95 *D* in benzene solution) for example, in comparison with aliphatic nitro compounds (3·3 *D*), is considered as the effect of polar structures such as II and III, while the reduced moment of nitromesitylene (3·67 *D*), in comparison with nitrobenzene, is taken as evidence for steric inhibition of resonance due to deviations from coplanarity—deviations which our recent X-ray work has indicated are real. These figures suggest however that at most 40 per cent of the dipole moment differences is the result of other valence structures, the remainder being presumably due to differences in hybridization or inductive effects, probably both. The X-ray analysis of nitromesitylene indicates that the moments of the methyl groups probably do not cancel (as is assumed in the above discussion of resonance effects) since the bond angles at the methyl groups differ significantly from 120°, and also that the valency angles around the nitro group differ from the values in nitrobenzene. All these variations would have to be taken into account before the small difference of 0·28 *D* could be considered as the effect of resonance involving ionic structures.

Further consideration of this type of physical property is obviously desirable.

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A THEORETICAL STUDY OF THE CHEMISTRY OF ISOQUINOLINE

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Abstract—A Hückel molecular-orbital treatment of isoquinoline, analogous to previously published treatments of quinoline and of some five-membered ring heterocycles, is presented. It is shown that the apparently anomalous orientations observed in some electrophilic substitution reactions can be explained in terms of the molecular-orbital results. A new mechanism, similar to that previously proposed for some electrophilic substitutions in quinoline, is proposed to account for the orientation of bromination and mercuration of isoquinoline.

The high reactivity of the 1- and 3-positions of isoquinoline towards nucleophils is also predicted by the theoretical results. Radical attack is briefly considered also.

The values of parameters found appropriate in a previous study of quinoline are confirmed by the present work. Bounds for an additional parameter relating to the energy of a localized π-electron adjacent to a heteroatom are indicated by the present analysis.

CONSIDERABLE progress has been made recently in elucidating the chemical properties of some nitrogen and oxygen heterocycles. On the one hand mechanisms of some substitution reactions have been investigated[1–3] and more precise observation of the orientation of some electrophilic substitutions have been reported.[4–9] On the other hand the analysis of chemical properties in the light of simple Hückel molecular-orbital calculations, which suggested the possibility of preliminary protolysis of secondary nitrogen in certain cases,[10,11] and protonation of tertiary nitrogen in others,[12–14] has provided a basis for interpretation of many apparently anomalous observations.[13–15] Some new reaction mechanisms have also been suggested as a consequence of these studies.[4,13,14] In addition values of the hetero-parameters which occur in the Hückel method have been settled to within narrow limits in this work[14,15] and these values are in good agreement with independent theoretical estimates[16] based on the variable-electronegativity-self-consistent-field molecular orbital method. The present theoretical study of the chemistry of isoquinoline can therefore be based largely on values of the Hückel parameters already established.

[1] R. D. Brown, H. C. Duffin, J. C. Maynard and J. H. Ridd, *J. Chem. Soc.* 3937 (1953).
[2] J. H. Binks and J. H. Ridd, *J. Chem. Soc.* 2398 (1957).
[3] R. D. Brown, B. A. W. Coller and M. L. Heffernan, *J. Chem. Soc.* 1776 (1958).
[4] M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.* 944 (1957).
[5] M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.* 2521 (1957).
[6] M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.* 345 (1957).
[7] M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.* 3079 (1958).
[8] P. B. D. de la Mare, M. Kiamud-Din and J. H. Ridd, *Chem. & Ind.* 361 (1958).
[9] R. D. Brown, unpublished experiments.
[10] I. M. Bassett and R. D. Brown, *J. Chem. Soc.* 2701 (1954).
[11] R. D. Brown, *Aust. J. Chem.* **8**, 100 (1955).
[12] R. D. Brown and M. L. Heffernan, *J. Chem. Soc.* 4288 (1956).
[13] R. D. Brown, *Current Trends in Heterocyclic Chemistry* p. 13. Butterworths, London (1958).
[14] R. D. Brown and R. D. Harcourt, *J. Chem. Soc.* In press.
[15] R. D. Brown and B. A. W. Coller, *Aust. J. Chem.* **12**, 152 (1959).
[16] R. D. Brown and M. L. Heffernan, *Aust. J. Chem.* **12**, 319 (1959).

Previous molecular-orbital studies of isoquinoline[5,17,18] were based on parameter values now considered to be unsatisfactory and are not nearly as detailed as the present investigation.

METHOD

Details of the method have been set out previously.[14,15] Values of π-electron densities and localization energies were computed as functions of the coulomb parameter h and the auxiliary inductive parameter h' of the nitrogen atom. The CN resonance integral was assigned the standard value β° because previous studies have shown that π-electron densities are insensitive to the value of this integral and only for positions adjacent to the heteroatom are the localization energies appreciably dependent upon its value.

As has previously been mentioned[14] the value to be assigned to the energy of a localized electron when computing localization energies at positions adjacent to heteroatoms is uncertain. If the auxiliary inductive effect is still fully operative at localized centres then the value $\alpha^\circ + h'\beta^\circ$ is appropriate, if it is no longer operative then the value α° is appropriate. Wheland[19] has suggested that some intermediate value should be used and the quantum mechanical mechanism currently envisaged for the auxiliary inductive effect[16] implies an intermediate value since localization will probably considerably reduce the value of the nearest neighbour electron repulsion integral $\gamma_{\mu\nu}$. The present investigation provides the first direct evidence, based on prediction of chemical properties, that such intermediate values should be assigned to energies of localized electrons.

RESULTS AND DISCUSSION

(a) *Electrophilic substitution*

Two main types of orientation of electrophilic substitution have been observed experimentally. Bromination[20,21] and mercuration[22] lead to 4-substituted isoquinolines while in concentrated sulphuric acid sulphonation[23] and nitration[5] yield mainly 5-substituted quinolines, with the 8-substituted quinolines as minor products. From the calculated π-electron densities (Figs. 1 and 2) neither of these orientations can be reconciled with direct substitution in the free base because for physically acceptable values of the coulomb parameters the expected order of reactivity is $5 > 7 >$ others. The electrophilic localization energies for the free base (Figs. 3 and 4) can be reconciled with 5,8-orientation but from our studies on quinoline[14] it seems probable that the isoquinolinium cation is the reacting species when this orientation is observed. The preferential attack at the 4-position can however be explained in terms of a mechanism similar to that proposed to explain 3-substitution in quinoline.[14] Preliminary 1:2-addition of EB (electrophil and nucleophil) produces a 1:2-dihydroisoquinoline system, the charge densities for this being shown in Figs. 5 and 6. This would be expected to be attacked by electrophils preferentially at the 4-position. On this basis

[17] H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.* **43**, 87 (1947).
[18] I. Samuel, *C.R. Acad. Sci., Paris* **236**, 2510 (1953).
[19] G. W. Wheland, *J. Amer. Chem. Soc.* **64**, 900 (1942).
[20] J. J. Padbury and H. G. Lindwall, *J. Amer. Chem. Soc.* **67**, 1268 (1945).
[21] F. W. Bergstrom and J. H. Rodda, *J. Amer. Chem. Soc.* **62**, 3030 (1940).
[22] T. Ukai, *Chem. Abstr.* **25**, 5427 (1931).
[23] F. T. Tyson, *J. Amer. Chem. Soc.* **61**, 183 (1939).

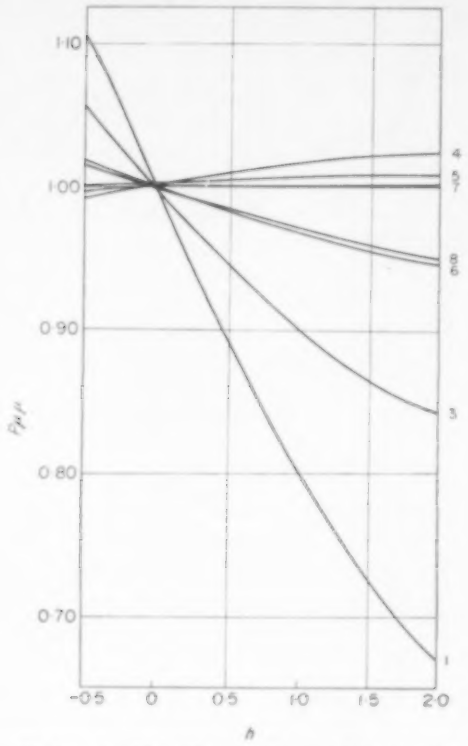


FIG. 1. π-Electron densities of isoquinoline as a function of h (for $h' = 0$).

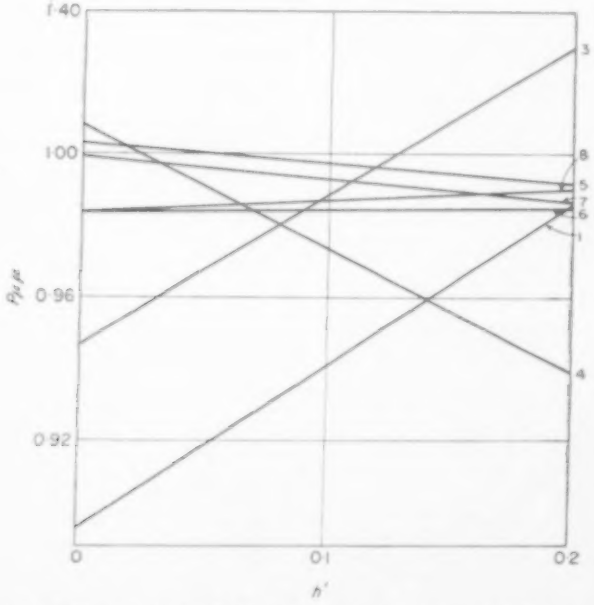


FIG. 2. π-Electron densities of isoquinoline as a function of h' (for $h = 0{\cdot}5$).

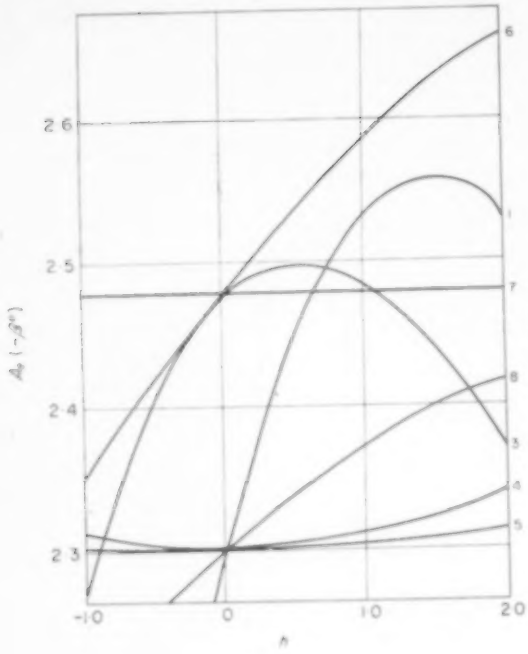


FIG. 3. Electrophilic localization energies of isoquinoline as a function of h (for $h' = 0$).

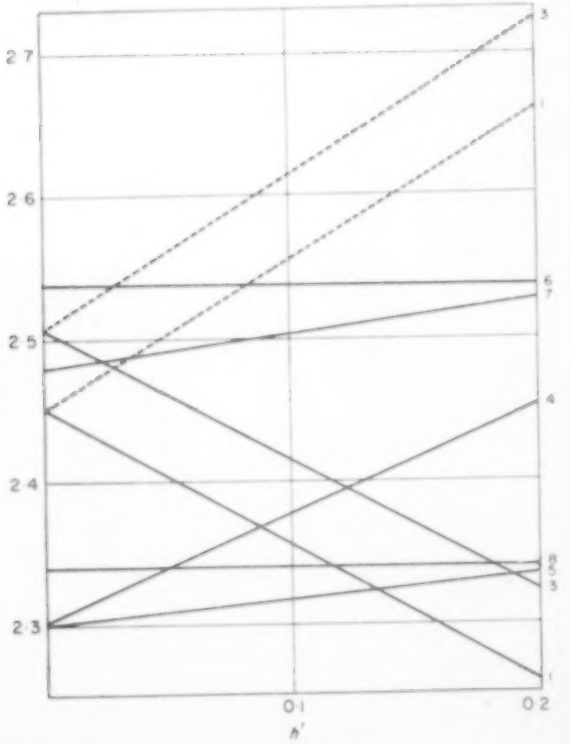


FIG. 4. Electrophilic localization energies of isoquinoline ($h = 0{\cdot}5$) as a function of h'. (For positions 1 and 3: Broken line, $\delta = 0$; full line $\delta = 1$.)

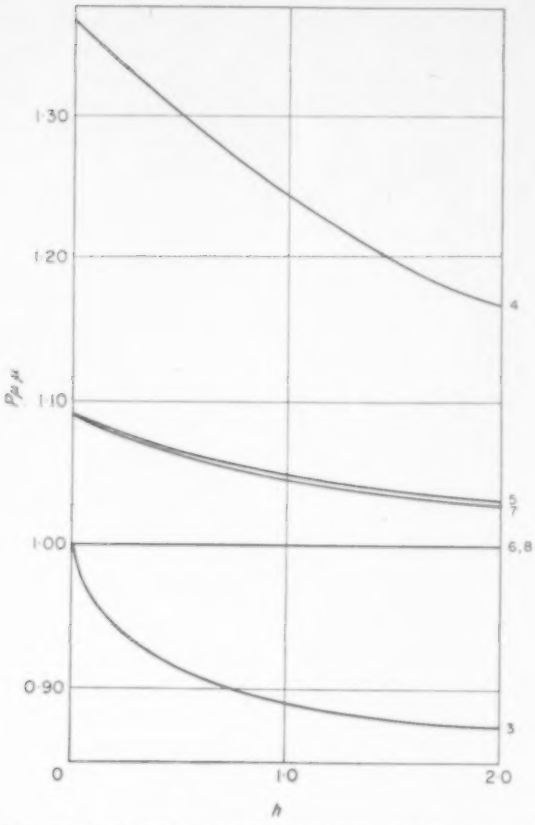


FIG. 5. π-Electron densities of 1:2-dihydroisoquinoline as a function of h (for $h' = 0$).

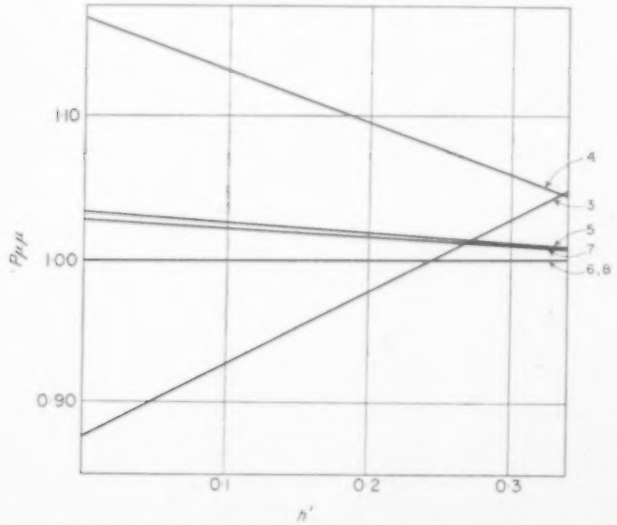
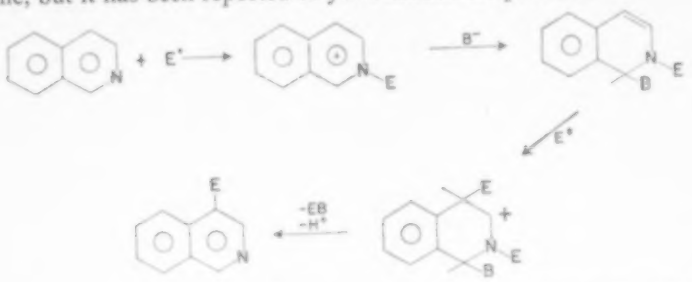


FIG. 6. π-Electron densities of 1:2-dihydroisoquinoline as a function of h' (for $h = 2$).

we should expect the nitration of isoquinoline in acetic anhydride to yield 4-nitroisoquinoline, but it has been reported to yield intractable products.[4]



In concentrated sulphuric acid the concentration of free base is probably too low for it to take a significant part in the reaction, the relatively unreactive isoquinolinium cation being the species probably undergoing substitution. The orientation might therefore be expected to be predicted by electrophilic localization energies rather than

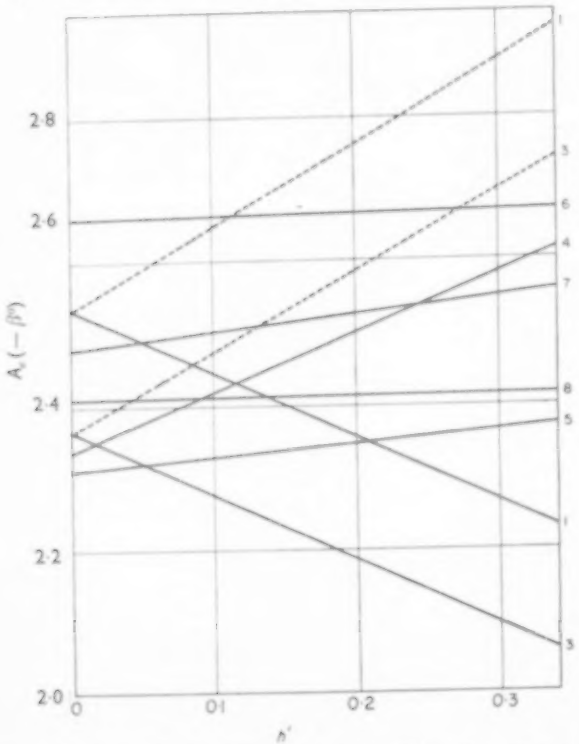


FIG. 7. Electrophilic localization energies of isoquinolinium ($h = 2$) as a function of h'. (For positions 1 and 3: Broken line, $\delta = 0$; full line, $\delta = 1$.)

by π-electron densities.[13,14] Electrophilic localization energies are shown in Figs. 3 and 7 and for physically acceptable values of the coulomb parameters ($h = 2$, $h' = 0{\cdot}2$–$0{\cdot}25$) predict the reactivity order $5 > 8 >$ others provided that the energy of an electron localized at the 1 or 3 positions is taken as $\alpha^{\circ} + \delta h'\beta^{\circ}$ where $\delta < 0{\cdot}43$. Thus

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if the general reliability of the simple Hückel method is accepted we now have a definite indication of the upper limit for δ, confirming Wheland's suggestion[19] that δ should be appreciably less than unity.

(b) *Nucleophilic attack*

Attack by nucleophils on isoquinoline always occurs primarily at the l-position[24–26] and a methyl substituent is most reactive towards benzaldehyde and analogous reagents when at the l-position, a methyl substituent at the 3-position being next

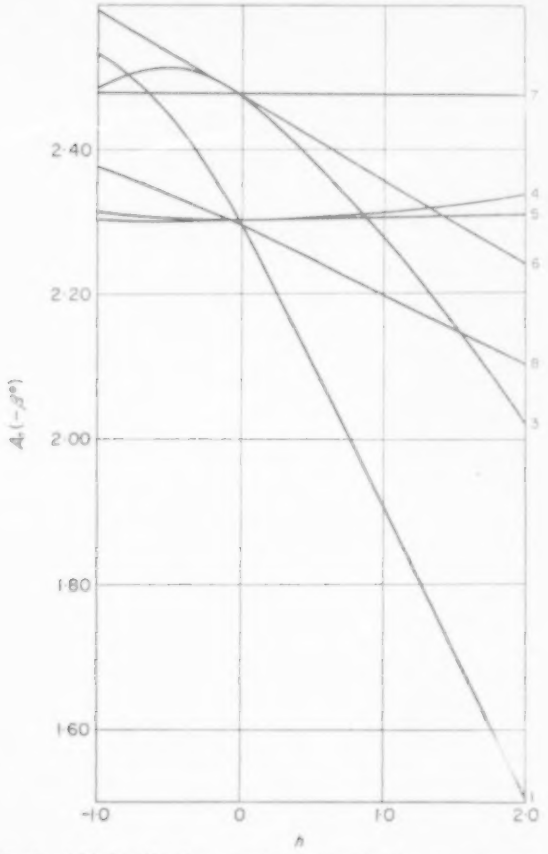

FIG. 8. Nucleophilic localization energies of isoquinoline as a function of h (for $h' = 0$).

in reactivity.[27,28] Although there is some small uncertainty as to whether these attacks occur on the free base or on "electrophilated" isoquinoline (see discussion of comparable problem for quinoline[14]) the relative reactivities point to an order of π-electron densities of $1 < 3 <$ others and this order is found in the molecular-orbital calculations

[24] F. W. Bergstrom, *Liebigs Ann.* **515**, 34 (1934); *J. Org. Chem.* **2**, 414 (1937).
[25] F. W. Bergstrom and S. H. McAllister, *J. Amer. Chem. Soc.* **52**, 2845 (1930).
[26] A. E. Tschitschibabin and A. I. Kursanova. *Chem. Abstr.* **25**, 2727 (1931).
[27] W. H. Mills and J. L. B. Smith, *J. Chem. Soc.* **121**, 2724 (1922).
[28] H. Erlenmeyer, H. Baumann and E. Sorkin, *Helv. Chim. Acta* **31**, 1978 (1948).

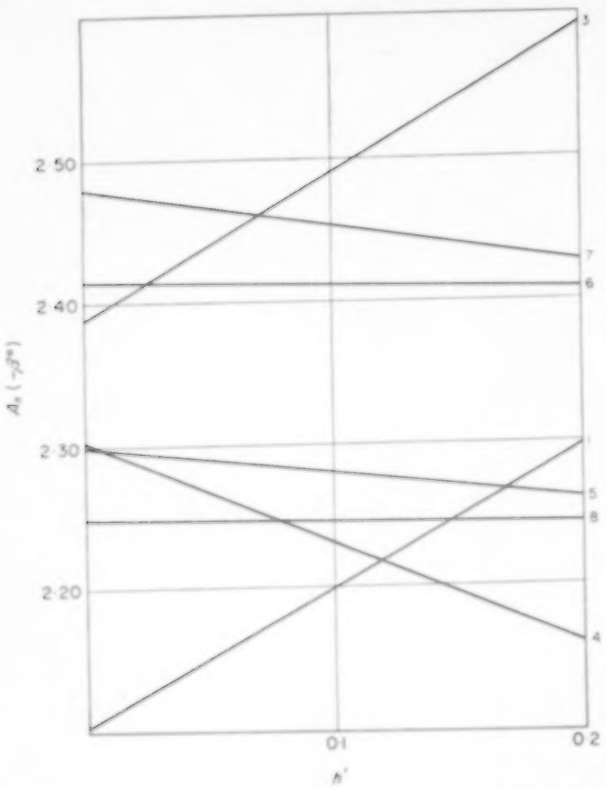

FIG. 9. Nucleophilic localization energies of isoquinoline ($h = 0{\cdot}5$) as a function of h'.

for both isoquinoline and the isoquinolinium cation (Figs. 1 and 2). N-alkylisoquinolinium ions are also attacked by nucleophils preferentially at the 1-position[29,30] and methyl substituents in the 1-position and, to a lesser extent, at the 3-position react with aldehydes.[27,28] This accords with the calculated π-electron densities for the isoquinolinium system.

Nucleophilic localization energies for isoquinoline and the isoquinolinium cation are shown in Figs. 8, 9 and 10.

(c) *Radical attack*

Radical localization energies for isoquinoline are shown in Figs. 11 and 12. There is no clearcut experimental evidence on the orientation of radical attack, but vapour phase bromination, which may involve radical attack by bromine atoms, yields 1-bromoisoquinoline.[31] This orientation is in agreement with the localization energies for physically reasonable values of h and h' provided that the "localized energy" parameter δ is greater than 0·80 (for $h = 0{\cdot}5$, $h' = 0{\cdot}085$). This is a greater value than was required when considering electrophilic substitution but clearly this value is likely to vary with the nature of the localizing entity.

[29] M. Freund, *Ber. Dtsch. Chem. Ges.* **37**, 4666 (1904).
[30] M. Freund and G. Bode, *Ber. Dtsch. Chem. Ges.* **42**, 1746 (1909).
[31] H. E. Jansen and J. P. Wibaut, *Rec. Trav. Chim.* **56**, 699 (1937).

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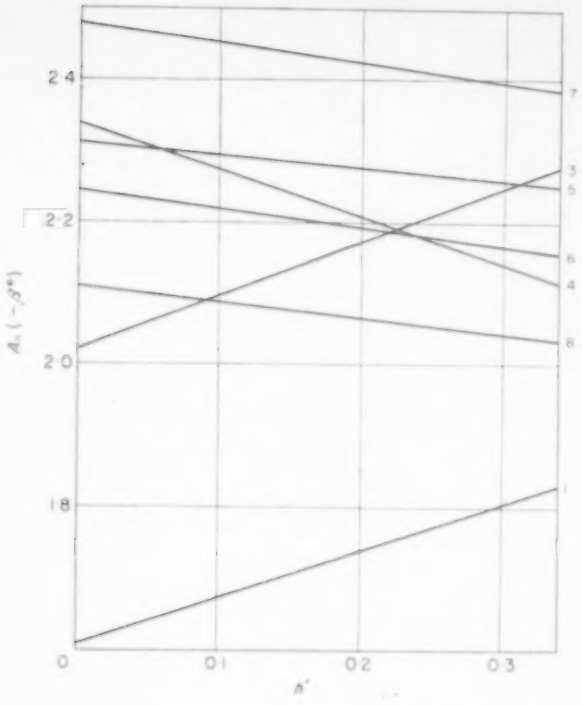

FIG. 10. Nucleophilic localization energies of isoquinolium ($h = 2$) as a function of h'.

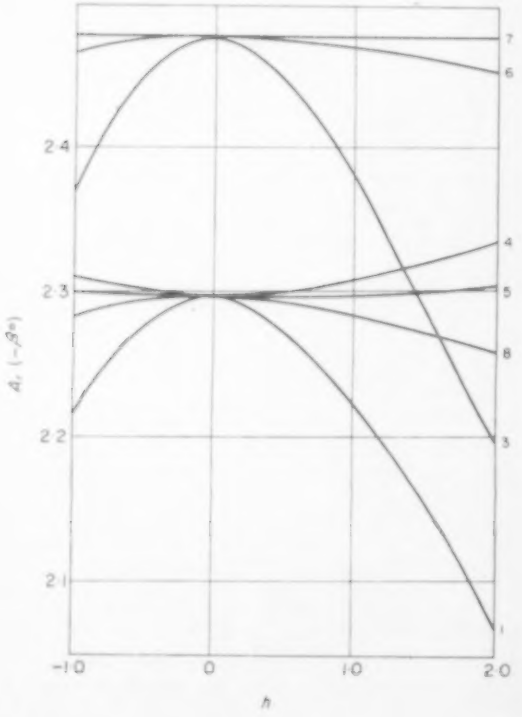

FIG. 11. Radical localization energies of isoquinoline as a function of h (for $k = 0$).

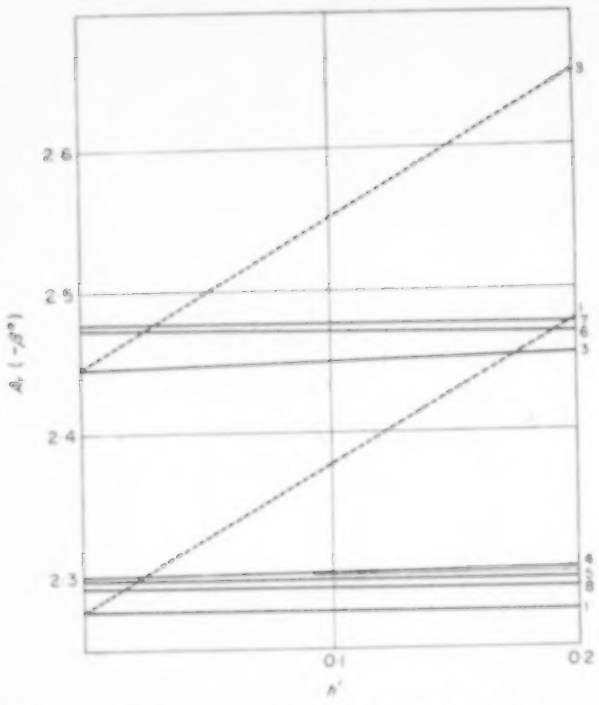

FIG. 12. Radical localization energies of isoquinoline ($h = 0{\cdot}5$) as a function of h'. (For positions 1 and 3: Broken line, $\delta = 0$; full line, $\delta = 1$.)

CONCLUSION

It has been possible to account fully for the observed chemistry of isoquinoline in terms of simple Hückel MO calculations and using values of the heteroparameters similar to those found suitable for interpreting the chemistry of other heterocycles. In fact these values of parameters have now been tested sufficiently to suggest that they should be suitable for theoretical treatments of other nitrogen heterocycles, the values being

$$\beta^{\circ}_{CN} = \beta^{\circ}$$
tertiary N: $h = 0{\cdot}5,\ h' = 0{\cdot}085$
secondary N: $h = 2,\ \ h' = 0{\cdot}2.$

In addition some more definite indications of the appropriate procedure for computing localization energies for positions adjacent to heteroatoms have been obtained. These do not affect our previous study of quinoline because the position adjacent to the quinoline nitrogen (the 2-position) plays no part in electrophilic substitution while localization energies for nucleophilic substitution do not incorporate the energies of electrons localized at the 2-position. The vapour phase bromination of quinoline was tentatively interpreted in terms of radical localization energies for the quinolinium system and, as in the present case of vapour phase bromination of isoquinoline, the lowest localization energy is found for the observed position of bromination provided that the value used for δ is not too small.

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NEW MUTUAL CONVERSION OF AROMATIC SYSTEMS

TROPILIUM SALTS AND BENZENE

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Abstract—The present work reports on the effected direct conversion of the aromatic tropilium cation to benzene and that of benzene to tropilium cation.

NUMEROUS rearrangements of tropone and tropolone derivatives[1] as well as oxidation of tropilium salts with chromic acid or silver oxide[2] give rise to substituted benzene with the same number of carbon atoms as in the parent compound.

We have recently discovered a reaction of direct conversion of tropilium salts to unsubstituted benzene accompanied by elimination of one carbon atom.

The formation of benzene from tropilium takes place under the action of aqueous hydrogen peroxide at room temperature, the main products of the reaction other than benzene being carbon monoxide and formic acid (almost in equal amounts). See Table 1.

The process is seen to be going mainly in two directions:

We have investigated the kinetics of the former reaction (accompanied by evolution of carbon monoxide). It follows a second order equation with a second order velocity constant (at 20·05° in aqueous solution) 10·4 ± 0·3 l. mole^{-1} min^{-1}. The Arrhenius parameters over the 20–50° range are E 10·5 kcal/mole, lg A 8·89.

Considerably increasing the acidity of the media (if the reaction is carried out in 1 N H_2SO_4) only negligibly reduces the reaction rate (velocity constant 7·7 at 20°). The reaction stops already in slightly alkaline media, that is under the conditions when, according to Doering and Knox,[3] the tropilium ion concentration sharply falls due to the right hand shift of the equilibrium $C_7H_7^+ + 2H_2O \rightleftarrows C_7H_7OH + H_3O^+$. In passing from aqueous to alcoholic solutions the reaction rate increases by one order, possibly owing to the tropilium ion being less solvatized. Substituting perchlorate for tropilium bromide does not affect the reaction course.

[1] P. Pauson, *Chem. Rev.* **55**, 9 (1955).
[2] W. E. Doering and L. H. Knox, *J. Amer. Chem. Soc.* **79**, 352 (1957).
[3] W. E. Doering and L. H. Knox, *J. Amer. Chem. Soc.* **76**, 3203 (1954).

The reaction of tropilium salts with hydrogen peroxide does not appear to involve free radicals. Thus, equimolecular addition of ferric sulphate and sulphuric acid (favouring the hydrogen peroxide and organic peroxide decomposition into free radicals) markedly hinders the reaction, the rate falling two to threefold and the

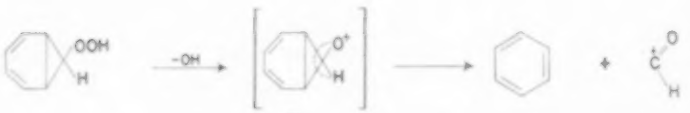
TABLE 1

	g-mole	Calc. for C_7H_7Br (%)
Starting compounds		
$C_7H_7^+Br^-$	0·0780	100
H_2O_2	0·0780	100
Reaction products		
C_6H_6	0·0644	82·5
CO	0·0393	50·4
HCOOH	0·0390	50·0
C_6H_5CHO		(~1·0)
C_6H_5OH		(~0·1)

termination of the reaction necessitating a considerable excess of hydrogen peroxide.

The data obtained suggest the first bimolecular reaction step to proceed due to the reaction of the tropilium ion and hydrogen peroxide to yield unstable hydroperoxide (I) that either directly decomposes into reaction products, or is first converted into cation II to be split into benzene and cation HCO^+ as follows:

I



II

$$H\overset{+}{C}{=}O \longrightarrow H^+ + CO, \quad H\overset{+}{C}{=}O + H_2O \longrightarrow HCOOH + H^+$$

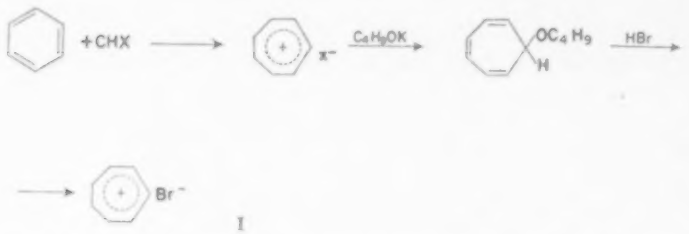
One could have also thought the reaction to proceed via the intermediate formation of tropone. But tropone does not decompose into benzene and carbon monoxide, neither does it react with hydrogen peroxide under studied conditions. Similar considerations lead to suggest that the reaction does not proceed through benzaldehyde as an intermediate. It will be seen that the above cycle contraction reaction is characterized by a simultaneous cleavage of two C—C bonds to give an unsubstituted benzene ring.

It seemed of interest to effect the reverse conversion of benzene directly to tropilium cation. To this end we attempted to add dihalocarbenes CCl_2 and CBr_2 to

benzene but the Doering and Hoffmann's reaction of $CHCl_3$ and CHBr with potassium t-butylate[4] when carried out in the presence of benzene did not yield the expected tropone.

Believing our failure to be due to the activity of dihalocarbenes CX_2 not being high enough and bearing in mind that unsubstituted methylene readily adds on to benzene we postulated that monohalocarbenes CHX could readily react with benzene. Indeed, we succeeded in showing that the reaction of methylene chloride, bromide or iodide with potassium t-butylate in benzene leads in all cases to tropilium salts, though in poor yields. This may be accounted for by the formation of monohalocarbenes as intermediates and their reaction with benzene, according to the following scheme:

$$CH_2X_2 + C_4H_9OK \longrightarrow CHX + C_4H_9OH + KX$$



I

with X being Cl, Br or I. The tropilium salt thus formed reacts with potassium *tert.*-butylate to give butoxycycloheptatriene that, in turn, leads to tropilium bromide when treated with hydrogen bromide. The concentration of starting compounds and the reaction time do not essentially affect the tropilium salt yield, the temperature rise somewhat increasing it.

There are no indications in the literature on the formation of unsubstituted monohalocarbenes. According to Hine *et al.*[5] the reaction of methylene halides and sodium methoxide in methanol follows the S_N2 mechanism, alcoholysis proceeding successively faster in the following sequence $CH_2Cl_2 < CH_2Br_2 < CH_2I_2$. On the other hand the tropilium salt yield rises in a reverse order, or $CH_2I_2 < CH_2Br_2 < CH_2Cl_2$. This is in accordance with the data obtained by Hine[6] on the readiness of dihalocarbene formation from haloformes depending on the halogen ($I < Br < Cl$). The evidence obtained allows us to suggest that alcoholysis of methylene halides by potassium t-butylate partly proceeds with intermediate formation of monohalocarbenes that may add to benzene to give tropilium derivatives.

EXPERIMENTAL

To a solution of tropilium bromide (13·34 g, 0·0780 mole) in water (100 cc) with cold water cooling, 5% hydrogen peroxide was added. An equivalent amount of hydrogen peroxide having been added, the solution contained no tropilium bromide, as evidenced by absence of precipitate when adding chloroplatinic acid solution.[7] Stirring was continued for 30 more min and the reaction mixture extracted with n-octane (previously distilled on a column). As to the aqueous solution (A) see below.

Organic extracts were washed with water, 10% NaOH, again with water, dried with magnesium

[4] W. E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.* **76**, 6162 (1954).
[5] J. Hine, C. H. Thomas and S. J. Eherenson, *J. Amer. Chem. Soc.* **77**, 3886 (1955).
[6] J. Hine, D. C. Duffy, P. B. Langford and J. J. Porter, *Angew. Chem.* **69**, 682 (1957).
[7] M. E. Volpin, S. I. Zhdanov and D. N. Kursanov, *Dokl. Akad. Nauk SSSR* **112**, No. 2, 264 (1957).

sulphate, and distilled on the column (10 theoretical plates), 4·90 g benzene being obtained, b.p. 79·6–80·1°/746 mm, n_D^{20} 1·5005.

(Found: C, 92·14, 92·12; H, 7·71, 7·81. C_6H_6 requires: C, 92·21; H, 7·74%).

The intermediate fraction (0·95 g), b.p. 80·1–123°, n_D^{20} 1·4123, contains additional 0·12 g benzene, the overall benzene yield amounting to 5·02 g (82·5%).

Benzene was identified by ultra-violet spectrum and nitration (with mixture of H_2SO_4 and HNO_3) to nitrobenzene to give further aniline by zinc dust reduction in HCl. Aniline was converted into benzanilide, m.p. 160–161°. (lit. m.p. 162°). The mixed melting point with the authentic sample showed no depression.

Aqueous solution. (A) was vapour distilled, the distillate containing 0·0390 mole formic acid (as ascertained by potassium permanganate titration), the latter identified as *p*-bromophenacyl ester, m.p. 141–142° (lit. m.p. 142°) showed no melting point depression with the authentic sample.

The reaction was accompanied by evolution of 1000 cc gas (at 19·6°/746 mm over NaCl saturated solution) that contained 98·6% CO and 1·4% O_2, the latter apparently at the expense of the partial decomposition of hydrogen peroxide.

Reaction of tropilium perchlorate and hydrogen peroxide

To 9·8 g of tropilium perchlorate (0·05 mole) 25% H_2O_2 (8 cc) in water (30 cc) was gradually added with cooling, and the reaction mixture extracted with ether. The extracts were washed with 10% alkaline solution (as to treatment of alkaline extracts see below) and water, dried over magnesium sulphate and distilled, yield 2·8 g (72%) benzene, b.p. 79·7–78·1°, n_D^{20} 1·5005, d_4^{20} 0·8748. The residue from distillation of benzene was dissolved in alcohol and 2,4-dinitrophenyl hydrazine alcoholic solution added to precipitate 2,4-dinitrophenylhydrazone benzaldehyde (0·11 g or 1%), m.p. 237° (lit. m.p. 237°); the mixed melting point determination with the authentic sample showed no depression.

The alkaline extracts (see above) were evaporated to a small volume, acidified and treated with iodine in potassium iodide solution and with soda. The precipitate was triiodophenol (0·11 g, 0·1%, m.p. 157–158°, lit. m.p. 157°); the mixed melting point determination with the authentic sample showed no depression.

The reaction yielded 820 cc CO (740·4 mm at 20·7° over saturated NaCl solution), or 0·031 mole (62%).

Kinetic study of the reaction of tropilium bromide and hydrogen peroxide

Equimolecular aqueous solutions of hydrogen peroxide and tropilium bromide were placed in a thermostat and vigorously shaken, the reaction rate being followed by the volume of the evolving gas (CO). It has previously been shown that the amount of gas formed (when shaken) is proportional to the amount of the reacted substances. The rate constant was calculated from the equation:

$$K = 1/tC_0(V_t/V_\infty - V_t)$$

where t is the time from the beginning of the reaction

V_∞—the amount of gas evolved after the end of the reaction (determined experimentally),

V_t—the amount of gas evolved measured in time,

C_0—initial concentration of reacting substances

To evaluate K use was made of the value V_t from the beginning of the reaction up to 60–70% conversion. Arrhenius parameters were evaluated over a 10–15° range in terms of $K_{10\text{-}0^\circ} = 6{\cdot}12$, $K_{20\text{-}00^\circ} = 10{\cdot}4$, $K_{20\text{-}0^\circ} = 20$, $K_{30\text{-}0^\circ} = 33$ and $K_{50\text{-}0^\circ} = 61{\cdot}5$.

Reaction of benzene and methylene chloride

(a) To the boiling mixture of 8·4 g (0·075 mole) dry potassium t-butylate (not containing t-butyl alcohol) and absolute benzene (200 cc) 19·1 g (0·225 mole) methylene chloride were added with stirring. After addition, the mixture was stirred for 4 hr at 60° and left overnight. The solidified brownish mass was filtered off, the filtrate evaporated in vacuum and swept with dry hydrogen bromide. The precipitate was filtered off, washed with absolute benzene and dried in vacuum. The reaction yielded 0·24 g tropilium bromide. (1·9% accounted for by potassium t-butylate).

The substance obtained is soluble in water and after treating with sodium bicarbonate and benzene extraction is again precipitated by hydrogen bromide. Under the action of H_2PtCl_6 tropilium chloroplatinate is precipitated from the aqueous and alcoholic solutions. The infra-red and ultra-violet spectra of tropilium bromide are identical to those obtained by Doering and Knox.[8]

(b) To the mixture of 10·7 g (0·095 mole) potassium t-butylate and benzene (200 cc) 15·3 (0·18 mole) CH_2Cl_2 were added (30 min) at room temp with stirring. The reacting substance was stirred for seven days, the precipitate then filtered off and the filtrate swept with dry hydrogen bromide. The precipitate was treated with water and the aqueous solution made alkaline with sodium bicarbonate. The ditropyl ether was extracted with benzene. Sweeping the benzene solution with hydrogen bromide yielded tropilium bromide, (0·16 g, yield 1·4%).

Reaction of benzene and methylene bromide

(a) 8·9 g (0·08 mole) potassium t-butylate, 27·8 g (0·16 mole) CH_2Br_2 and benzene (200 cc) at room temp (under experimental conditions as above) resulted in 0·06 g tropilium bromide (yield 0·44%).

(b) 11·2 g (0·1 mole) potassium t-butylate, 22·6 g (0·13 mole) CH_2Br_2 and benzene (200 cc) under reflux gave 0·20 g of tropilium bromide (yield 1·2%).

Reaction of benzene and methylene iodide

10·3 g (0·09 mole) potassium t-butylate, 44·4 g (0·17 mole) CH_2I_2 and benzene (200 cc) at room temp yielded to 0·015 g tropilium bromide (yield 0·1%).

Tetrahedron, 1960, Vol. 8, pp. 38 to 41. Pergamon Press Ltd. Printed in Northern Ireland

POLYFLUORO-AROMATIC COMPOUNDS—III*

TETRA- AND TRI-FLUORO-*p*-BENZOQUINONE

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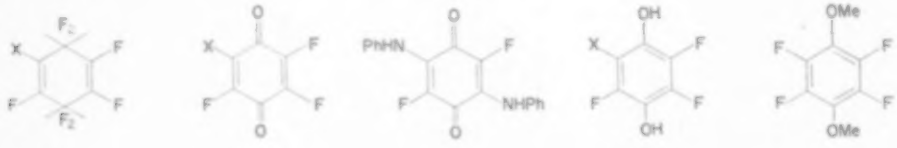
(*Received* 25 *July* 1959)

Abstract—Octafluorocyclohexa-1:4-diene gave, with oleum, tetrafluoro-*p*-benzoquinone which was reduced to the corresponding hydroquinone derivative, the dimethyl ether of which is identical with that formed from hexafluorobenzene and sodium methoxide. 1H-Heptafluorocyclohexa-1:4-diene gave 2:3:5-trifluorohydroquinone in a similar way.

IT is well-known in organic fluorine chemistry that an aromatic ring[1] or an olefinic bond[2] activates an adjacent trifluoromethyl group. In the former case, reaction with sulphuric acid followed by the addition of water converts $-CF_3$ into $-CO_2H$, benzotrifluoride itself giving benzoic acid. It appeared that the $>CF_2$ groups of fluorocyclohexadienes might be susceptible to similar types of attack. On treatment with fuming sulphuric acid at 100°, both $>CF_2$ groups of octafluorocyclohexa-1:4-diene[3] (I) were converted into $>C=O$. Though the primary product was probably a partly reduced quinone, after treatment with 50 per cent nitric acid, tetrafluoro-*p*-benzoquinone (II) was obtained in moderate yield. The quinone (II) was volatile, had a characteristic odour and oxidized iodide ion to iodine and N:N-dimethylaniline to methyl violet. It had ultra-violet and infra-red spectra consistent with its structure.



I, X = F
VI, X = H

II, X = F,
VII, X = H,

III

IV, X = F
VIII, X = H

V

The fluorine atoms in tetrafluoro-*p*-benzoquinone (II) are rather labile towards alkaline reagents. Aqueous sodium hydroxide caused liberation of fluoride ion, and aniline in ether attacked the quinone to give a compound which, by analogy with the products of similar reactions[4] of tetrachloro-*p*-benzoquinone, is probably 2:5-difluoro-3:6-di (phenylamino)-benzo-1:4-quinone (III). It is not surprising that the presence of four fluorine atoms in this quinone (II) renders the unsaturated carbon atoms carrying them more electropositive than usual and hence particularly susceptible to nucleophilic attack with subsequent loss of fluoride ion.

Tetrafluoro-*p*-benzoquinone (II) in diethyl ether was reduced with hydrogen–Raney

* Part II: *J. Chem. Soc.* 2019 (1959).

[1] G. M. Le Fave, *J. Amer. Chem. Soc.* **71**, 4148 (1949).
[2] A. L. Henne, M. A. Smook and R. L. Pelley, *J. Amer. Chem. Soc.* **72**, 4756 (1950).
[3] D. E. M. Evans and J. C. Tatlow, *J. Chem. Soc.* 3779 (1954); 1184 (1955).
[4] E. H. Huntress, *Organic Chlorine Compounds* p. 501. John Wiley, New York (1948).

nickel to give 2:3:5:6-tetrafluorohydroquinone (IV). Isolation without special precautions gave a hydrated form which, however, could be dried to give the anhydrous dihydric phenol. This was characterized also as its dibenzoate. With diazomethane the quinol gave tetrafluoro-*p*-dimethoxybenzene (V) which was identical with the dimethoxy-derivative obtained[5] by treatment of hexafluorobenzene with sodium methoxide in methanol. Thus, in this nucleophilic attack the second methoxy group enters the nucleus of 2:3:4:5:6-pentafluoroanisole in the position *para* to the first methoxy group.

1 H-Heptafluorocyclohexa-1:4-diene (VI) was prepared as before[6] and also by treatment of the octafluoro-1:4-diene (I) with lithium aluminium hydride in diethyl ether, a reaction used previously[6] to replace fluorine on a double bond by hydrogen. With fuming sulphuric acid this diene gave trifluoro-*p*-benzoquinone (VII), which, however, could not be obtained pure. Direct reduction of the reaction mixture gave 2:3:5-trifluorohydroquinone (VIII), characterized as its dibenzoate. Oxidation of the quinol (VIII) gave the quinone (VII) but this was too unstable for complete characterization.

Attempts to prepare tetrafluoro-*o*-benzoquinone from octafluorocyclohexa-1:3-diene[3] were unsuccessful. Though reaction of the diene with sulphuric acid occurred, isolation of either a quinone, or of a dihydric phenol by direct reduction of the crude reaction product, could not be accomplished.

After this work was done, Professor Wallenfels informed us of the preparation of tetrafluoro-*p*-benzoquinone by treatment of tetrachloro-*p*-benzoquinone with potassium fluoride, and of its conversion to the quinol and to the dimethyl ether of the last. Our two samples of the dimethoxide and Wallenfels' sample proved to be identical, affording useful confirmation of all the structures. Publication of Wallenfels' results[7] has revealed a minor discrepancy concerning the hydrate of the hydroquinone. Also, he reported[8] the formation of a tetra(phenylamino) quinone when tetrafluoro-*p*-benzoquinone was treated with aniline, presumably under more drastic conditions than ours.

EXPERIMENTAL

2:3:5:6-*Tetrafluoro*-p-*benzoquinone*. Octafluorocyclohexa-1:4-diene (16·0 g) was heated with vigorous shaking in a sealed tube at 100° with fuming sulphuric acid (20% SO_3; 50 cc) for 1½–2 hr. The reaction mixture was poured onto crushed ice (ca. 500 g) and the resulting solution was extracted continuously with ether for 72 hr. The ethereal extracts were dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in dry ether, the solution filtered and the ether evaporated. The residue was then oxidized with nitric acid (50% v/v; 50 cc), the resulting yellow precipitate filtered off, and purified by sublimation *in vacuo* to give 2:3:5:6-tetrafluorobenzoquinone (3·9 g), m.p. (sealed tube) 179°, (Found: C, 40·1; F, 41·9. Calc. for $C_6O_2F_4$: C, 40·0; F, 42·2%). Wallenfels and Draber[7] cited m.p. 179°.

The quinone (*c*. 0·00176 g/l. in n-hexane) showed two absorption maxima in the ultra-violet at 2465 Å and 2535 Å with ε_{max} 20,250 and 20,460 respectively. In the infra-red the compound showed a strong band at 1674 cm^{-1} characteristic of the quinone structure. The quinone was a volatile yellow crystalline solid with characteristic odour. It was a strong oxidizing agent, liberating iodine from potassium iodide and giving a deep violet colour with NN′-dimethylaniline. The fluorine atoms were extremely labile and treatment with very dilute alkali or organic bases liberated some fluoride ion.

Reaction of 2:3:5:6-*tetrafluorobenzoquinone with aniline*. The quinone (0·7 g), aniline (3 g) and dry

[5] J. A. Godsell, M. Stacey and J. C. Tatlow, *Nature, Lond.* **178**, 199 (1956).
[6] J. A. Godsell, M. Stacey and J. C. Tatlow, *Tetrahedron* **2**, 193 (1958).
[7] K. Wallenfels and W. Draber, *Chem. Ber.* **90**, 2819 (1957).
[8] K. Wallenfels and W. Draber, *Angew. Chem.* 313 (1958).

ether (30 cc) were shaken together at 20° for 1 hr. The deep brown precipitate was filtered off and recrystallized from dimethyl formamide to give shining black crystals of 2:5-*dianilino*-3:6-*difluorobenzoquinone* (1·0 g) m.p. 312° (decomp) (Found: C, 66·1; H, 3·9; F, 11·3. $C_{18}H_{12}O_2N_2F_2$ requires: C, 66·3; H, 3·7; F, 11·6%). Wallenfels and Draber[4] for—cited m.p. 310° but their reaction with aniline (no details quoted) gave 2:3:5:6-tetra-anilinobenzoquinone.

Reduction of 2:3:5:6-*tetrafluorobenzoquinone*. Tetrafluoro-*p*-benzoquinone (1·5 g) in dry diethyl ether (50 cc) was shaken at room temp. and atm. press. with Raney nickel and hydrogen for ca. 16 hr. The Raney nickel was filtered off and the filtrate evaporated to give a white solid (0·7 g). The crude solid was recrystallized from dry benzene to give white needles of 2:3:5:6-*tetrafluorohydroquinone* m.p. 168–169° (Found: C, 39·7; H, 1·2. $C_6H_2O_2F_4$ requires: C, 39·6; H, 1·1%).

Wallenfels and Draber[3] cited m.p. 166–167° for a compound which they claimed was hydrated. The infra-red spectrum of the above hydroquinone, however, showed it to be anhydrous. The hydroquinone, on standing in the atmosphere or on preparation using undried solvents, had m.p. 68–70° and showed a band at ca. 1640 cm^{-1} in the infra-red characteristic of the presence of water.

The anhydrous hydroquinone (*c*. 0·0044 g/l. in ethanol) showed two absorption maxima in the ultra-violet at 2130 Å and 2720 Å with ε_{max} 10,280 and 1406 respectively. In the infra-red the compound showed a strong absorption band at 1520 cm^{-1} characteristic of an aromatic ring.

The hydroquinone (0·1 g), benzoyl chloride (0·2 g) and pyridine (5 cc) were heated together for 5 min and cooled. The solution was poured into water, the precipitate filtered off, and washed with dil HCl, sodium carbonate solution and finally with water. The crude white solid was dried and recrystallized from ethyl alcohol to give 2:3:5:6-*tetrafluorohydroquinone dibenzoate* m.p. 157–158° (Found: C, 61·7; H, 2·7. $C_{20}H_{10}O_4F_4$ requires: C, 61·6; H, 2·6%).

1:4-*Dimethoxytetrafluorobenzene*. 2:3:5:6-Tetrafluoro-*p*-benzoquinone (1·0 g) in dry ether (50 cc) was shaken at room temp. and press. with Raney nickel and hydrogen for 16 hr. The Raney nickel was filtered off and the solution added to an ethereal solution of diazomethane at 0°. The reaction mixture was kept at 0–5° for 12 hr and then at 20° for a further 48 hr. The solution was filtered, evaporated and the residue recrystallized from aqueous methyl alcohol to give fine white needles of 1:4-dimethoxytetrafluorobenzene (0·5 g) m.p. 51–52° (Found: C, 45·9; H, 2·8. Calc. for $C_8H_6O_2F_4$: C, 45·7; H, 2·9%). Godsell *et al.*[5] cited m.p. 51·5–52·5°. The m.p. of the compound in admixture with that of Godsell *et al.* was 52° and the two compounds displayed identical infra-red spectra over the range 4000–700 cm^{-1}. The 1:4-dimethoxytetrafluorobenzene showed a band at 1500 cm^{-1} characteristic of an aromatic ring.

Reaction of lithium aluminium hydride with octafluorocyclohexa-1:4-*diene*. The diene (11·2 g) in dry ether (60 cc) was added rapidly to a stirred suspension of lithium aluminium hydride (1·8 g) in dry ether (200 cc) at −80°. Water (20 cc) was immediately added (cautiously) followed by sufficient aqueous sulphuric acid (50% v/v) to dissolve any remaining solid material. The ether layer was separated, dried ($MgSO_4$), filtered and evaporated through a 6 in. column packed with nickel gauzes. Separation of the product by preparative-scale gas chromatography (16′ × 3 cm column, dinonyl phthalate/kieselguhr 1:2, temp 80°, N_2 flow-rate 9·6 l/hr) gave:— (i) ether which was allowed to escape: (ii) 1H-heptafluorocyclohexa-1:4-diene (4·3 g), b.p. 67°, n_D^{18} 1·3288 (Found: C, 35·2; H, 0·6. Calc. for C_6HF_7; C, 35·0; H, 0·5%). Tatlow *et al.*[6] cited b.p. 66·5–67° and n_D^{16} 1·3275.

Reaction of 1H-*heptafluorocyclohexa*-1:4-*diene with sulphuric acid*. 1H-Heptafluorocyclohexa-1:4-diene (9·0 g) and fuming sulphuric acid (20% SO_3; 20 cc) were heated together in a sealed tube with vigorous shaking at 100° for 1½ hr. The reaction mixture was then poured onto crushed ice (ca. 300 g), zinc metal (15·0 g) was added and the mixture heated under reflux for 5 hr. The solution was cooled and extracted continuously with ether for 48 hr. The ether extract was dried ($MgSO_4$), filtered and evaporated in the presence of stannous chloride (2 g). The residue was sublimed at 90°/0·05 mm to give 2:3:5-*trifluorohydroquinone* (2·8 g), a white hygroscopic solid, m.p. 112–113° (in sealed tube) (Found: C, 44·0; H, 1·9. $C_6H_3O_2F_3$ requires: C, 43·9; H, 1·8%). The hydroquinone gave a violet colour with ferric chloride solution.

The hydroquinone (*c*. 0·0048 g/l. in ethanol) showed an absorption maximum in the ultra-violet at 2750 Å with ε_{max} 2187. In the infra-red the hydroquinone showed an absorption band at ca. 1500 cm^{-1} characteristic of an aromatic ring.

The hydroquinone (0·2 g), benzoyl chloride (0·5 cc) and dil aq NaOH were shaken mechanically together at 20° for 30 min. The reaction mixture was extracted several times with ether. The combined ethereal extracts were washed with sodium carbonate solution, dil HCl, water and dried ($MgSO_4$).

The extracts were evaporated and the residue recrystallized from ethanol to give 2:3:5-*trifluorohydroquinone dibenzoate* m.p. 80° (Found: C, 64·4; H, 2·9. $C_{20}H_{11}O_4F_3$ requires: C, 64·5; H, 2·9%).

Oxidation of 2:3:5-*trifluorohydroquinone*. Silver oxide, chromic oxide and conc HNO_3 all failed to convert the hydroquinone to the quinone.

The trifluorohydroquinone (1·0 g) was shaken mechanically at 20° for 1 hr with activated lead dioxide (3·0 g) and magnesium sulphate (1·5 g) in ether (50 cc). The solution was filtered and evaporated. The residue was sublimed *in vacuo* (ca. 70°/0·05 mm) to give the trifluoroquinone (0·1 g). The quinone was a bright yellow, hygroscopic solid but rapid decomposition in the atmosphere prevented characterization.

Acknowledgements—The authors thank Professor M. Stacey, F.R.S., for his interest in this work, the D.S.I.R. for a maintenance award (to E. N.), and Dr. D. H. Whiffen for the infra-red measurements.

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STUDIES IN SESQUITERPENES—XVII

HYDRATION OF LONGIFOLENE*†

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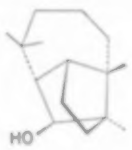
(*Received* 20 *May* 1959)

Abstract—Unlike the analogous case of camphene, hydration of longifolene with acetic acid–sulphuric acid in dioxane, yielded a strongly laevorotatory tricyclic isomer as the main product. At least three sesquiterpene alcohols resulted as side products, one of which could be correlated with longicamphor.

IN connexion with our attempts[1] to degrade longifolene (I) to a suitable azulene precursor, an easy route to longicamphor (III) was sought for. This ketone had been obtained previously by Naffa and Ourisson[2] by the oxidation of longiborneol (II), obtained from the corresponding longibornyl bromide via the Grignard derivative.

I



II

III

The preparation of longicamphor by this method appeared arduous, as the ketone could only be prepared in a poor (<15%) overall yield. Since camphene is known to yield isoborneol in an excellent yield on hydration with Bertram–Walbaum reagent,[3] this procedure appeared to be of great promise for the analogous preparation of longiborneol (II).‡ However, this reaction turned out to be a complex one and the chief product of the reaction was found to be an isomeric olefin, henceforth termed isolongifolene. This constituted ca. 60 per cent of the reaction product and the 'hydrated' material amounted to only ca. 30 per cent.§¶ The latter has been shown to consist of at least three acetates.

The acetate mixture resulting from the hydration of longifolene was saponified and the product fractionated to yield a liquid mixture of alcohols (ca. 89 per cent) and

* Presented at the Essential Oils & Aromatic Chemicals Symposium, Dehra Dun (India) October (1955).

† Abstracted from the Ph.D. thesis (Madras, 1957) of U. R. Nayak.

‡ Longifolene on hydrohalogenation gives only longibornyl halides [P. Ourisson and G. Ourisson, *Bull. Soc. Chim. Fr.* 1415 (1954)] in direct contrast with the case of camphene, which gives essentially only isobornyl derivatives. Likewise it may be anticipated that the hydration reaction would lead to longiborneol unlike camphene.

§ Naffa and Ourisson[2] also obtained similar results but did not examine the reaction products much further. These results were available to us after the publication of our preliminary note.[1]

¶ J. Tanaka and T. Aikawa [(*Rep. Osaka Ind. Res. Inst.* **30**, 141 (1955)] have also recently investigated this reaction and could isolate only one alcohol (m.p. 108–109°) besides isolongifolene. We are thankful to these authors for sending us (Aug. 1957) the above report.

[1] U. R. Nayak and Sukh Dev, *Chem & Ind.* 989 (1954).

[2] P. Naffa and G. Ourisson, *Chem. & Ind.* 917 (1953); *Bull. Soc. Chim. Fr.* 1410 (1954).

[3] J. Bertram and H. Walbaum, *J. Prakt. Chem.* [ii] **49**, 8 (1894).

a crystalline secondary alcohol (A; ca. 10 per cent) (m.p. 107–108°). Though the m.p. of this alcohol is almost the same as that reported for longiborneol (II, m.p. 106–107°), the substance was shown to be different (*vide infra*). The liquid mixture could only be separated by an indirect method. The mixture, after oxidation with chromic acid, could be separated by semicarbazide into reactive (ca. 60 per cent) and non-reactive (30 per cent) portions. The latter fraction (infra-red absorption: 3484 and 1715 cm^{-1}) could be separated by chromatography into a new crystalline tertiary alcohol (B: ca. 20 per cent) (m.p. 92–94°) and a pure hindered ketone (ca. 80 per cent).

The hindered ketone

Longicamphor (III). The unreactive ketone ($\nu^{C=O}$ 1715 cm^{-1}; liquid), from its method of preparation, was considered to be the desired longicamphor, which is known[2] to be a hindered ketone. On reduction with sodium and n-propanol it gave the crystalline longiborneol (II), which was identified by comparison with an authentic sample of the alcohol prepared from longibornyl bromide by the method of Naffa and Ourisson.[2] Lithium aluminium hydride reduction of the ketone, on the other hand, gave a liquid mixture of the epimeric alcohols which could not be separated either by chromatography over alumina or via the 3,5-dinitrobenzoates.

Reactive ketone and the solid alcohol (A)

The compound regenerated from the semicarbazone (once recrystallized; m.p. 210–214°) showed a broad, partially resolved carbonyl band in the infra-red spectrum (liquid), two peaks at 1700 and 1735 cm^{-1} and a shoulder at 1715 cm^{-1} being prominent. This would indicate a mixture of at least three reactive ketones and from the relative intensities of the peaks, the 1700 cm^{-1} ketone appeared to be the major

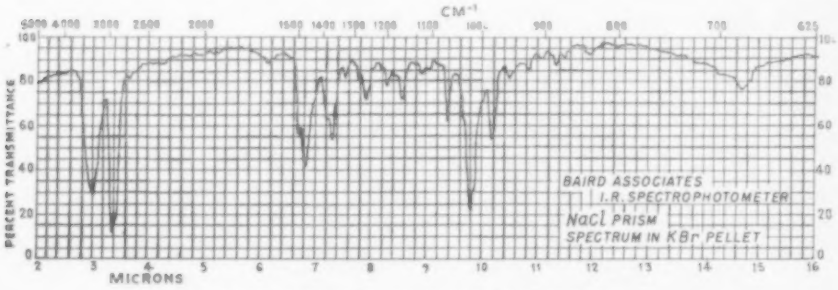


FIG. 1. Infra-red spectrum of solid alcohol (A).

component. When thoroughly purified semicarbazone (m.p. 215–216) was employed, the regenerated ketone was homogeneous and had a single peak in the carbonyl region at 1692 cm^{-1} (liquid). Reduction of this ketone with lithium aluminium hydride or with sodium-propanol gave a crystalline alcohol identified as the solid alcohol (A) by m.p. and mixed m.p. and also by preparing the 3,5-dinitrobenzoates which were identical. A further check was made by oxidizing the solid alcohol (A) when a single reactive ketone ($\nu^{C=O}$ 1692 cm^{-1}) was obtained. The infra-red spectrum of the alcohol is shown in Fig. 1.

The solid alcohol (B)

This compound was shown to be an alcohol from its absorption in the infra-red (Fig. 2) and since it resisted oxidation with chromic acid, it is presumably a tertiary alcohol. It was resistant to esterification and under the usual conditions failed to yield a 3,5-dinitrobenzoate.

*Isolongifolene**

By repeated fractionation of the isomerized hydrocarbon, isolongifolene could be isolated in a state of purity. The homogeneity of the product was checked by vapour-phase chromatography, when only a single non-resolvable peak was obtained. The hydrocarbon gives a yellow colour with tetranitromethane and it would appear from

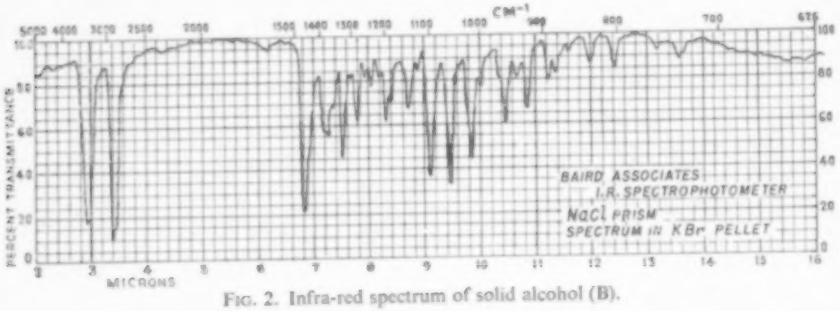


FIG. 2. Infra-red spectrum of solid alcohol (B).

its molecular refractivity (64·46) that isolongifolene is also tricyclic containing one ethylenic linkage. This was confirmed by quantitative hydrogenation over Adam's catalyst in acetic acid, when only one mole of hydrogen was absorbed to give a saturated hydrocarbon (negative tetranitromethane test). The infra-red spectrum of isolongifolane is quite different from that of longifolane, indicating a different carbon-skeleton for the hydrocarbon. In the C—H wagging region of the infra-red spectrum of isolongifolene a band at 820 cm^{-1} is the strongest and it would be reasonable to assign it to a trisubstituted olefinic linkage ($R_1R_2C = CHR_3$); it may be pointed out here that this band as well as a mild shoulder at 3050 cm^{-1} (=C—H stretching) are absent from the spectrum of isolongifolane. In the ultra-violet region, the new hydrocarbon showed only end absorption (ε_{210} 2180, ε_{215} 900, ε_{220} 265, ε_{225} 85) and this also is in accord with the occurrence of a trisubstituted ethylenic bond[4] in the molecule.

Preliminary work on these new products has shown that deep-seated rearrangements are involved and a systematic structure elucidation of isolongifolene has been taken up in this laboratory, in the first instance.

EXPERIMENTAL†

Isolation of (+)-longifolene

Pure longifolene was isolated from the 'Secondary Residue' obtained from the essential oil of *Pinus longifolia*, supplied by the Indian Turpentine & Rosin Co., Bareilly, U.P. (India).

* Recently J. Tanaka, [*Rep. Osaka Ind. Res. Inst.* No. 305 (1955); *Chem. Abstr.* **50**, 16708e (1956)] has reported the isomerization of longifolene with acetic acid–sulphuric acid to a new tricyclic hydrocarbon, which from its reported properties would appear to be identical with our isolongifolene.

† All melting and boiling points are uncorrected. The solvent extracts were dried over sodium sulphate. The infra-red spectra, unless otherwise stated, were determined by the Sadtler Research Laboratories, Philadelphia.

[4] P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.* 2737 (1952).

Secondary Residue (2754 g) was subjected to a preliminary fractionation through a helices-packed column (total condensation partial take-off type) and the main fraction (b.p. 116–120°/10 mm; $\alpha_D > +30°$; 2087 g) rich in longifolene was then systematically fractionated through another column* (30 theoretical plates). The rectification was carried out under reduced pressure (16 mm) employing a high reflux ratio (25 : 1). The charge was divided into 95 fractions and the course of fractionation was followed by observing the boiling point, refractive index and optical rotation for each fraction. By mixing the corresponding fractions of very similar properties three main cuts of the distillate were obtained: the earlier fraction (215 g), b.p. 117–126°/16 mm, having lower refractive index and rotation, the middle fraction (1241 g), b.p. 127–128°/16 mm, α_D +38° to +43·3° and the last fraction, (581 g), b.p. 129–139°/16 mm, $\alpha_D < +38°$. The second fraction (59%) which constituted pure longifolene was distilled over sodium and used for the present investigations. An analytical sample of longifolene had b.p. 118–119°/10 mm, n_D^{26} 1·5015, d_4^{26} 0·9319, M_D 64·71 (Calc. for $C_{15}H_{24}F_1$ 64·45), α_D +43·1° (homogeneous).

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Hydration of (+)-longifolene

By following the usual Bertram–Walbaum reaction, the 'hydrated' material could only be obtained in a poor yield (ca. 15%) and it required a series of experiments to determine the nearly optimum conditions of hydration. In these experiments the variables studied were the source of the anion (acetic acid, formic acid, chloracetic acid), a strong proton source (sulphuric acid, perchloric acid), solvent (dioxane, methyl cellosolve), catalyst, time and temperature.

The following experimental conditions were found to be most satisfactory. Longifolene (200 g), glacial acetic acid (500 ml) and sulphuric acid (50% v/v; 40 ml) were mixed and dioxane (475 ml) was added to get a homogeneous solution. The reaction mixture was kept at room temp (22–24°) for 61 hr, warmed to 50 + 2° for 10 hr and poured into water (600 ml). The organic layer was separated and the aqueous portion extracted with petroleum ether (50 ml × 3) after addition of ammonium sulphate. The oil was combined with the solvent extracts, washed with water till neutral, dried and the solvent removed through a column to obtain a deep brown liquid residue. The experiment was repeated with another lot (200 g) of longifolene and the crude hydration product obtained was combined with the earlier lot and fractionated to yield two products, isolongifolene and the acetate mixture. The former was obtained as a colourless mobile liquid, b.p. 119–122°/10 mm, n_D^{25} 1·4985, α_D −77°, yield 242 g (60·5%), and the latter distilled over as a colourless viscous liquid, b.p. 149–152°/9 mm, n_D^{25} 1·4925, d_4^{25} 1·001, M_D 76·52 (Calc. 75·76), α_D +26·9°, yield 154·6 g (29·9%) (Found: C, 77·53; H, 10·39. $C_{17}H_{28}O_2$ requires: 77·41; H, 10·61%).

Saponification of the mixed acetates

The above acetate mixture (154 g), potassium hydroxide (49 g) dissolved in water (30 ml) and ethanol (190 ml) were mixed and refluxed on the steambath (7½ hr). Most of the alcohol was then distilled off from the reaction mixture, the residue poured into water and the organic layer separated. The aqueous solution was extracted with pet. ether (50 ml × 3) and the combined organic portions were washed free of alkali with water, dried and the solvent removed through a column. The yellow residue (138 g) was carefully fractionated. After a small amount (4·45 g) of fore-run, the main fraction consisting of the liquid alcohol mixture distilled over as a colourless very viscous liquid, b.p. 147–149°/9 mm, n_D^{27} 1·5070 d_4^{27} 0·9946, M_D 66·41 (Calc. 66·4), α_D + 24° (c = 4·6%; ethanol), yield 114·8 g (88·6%) (Found: C, 81·2; H, 11·73. $C_{15}H_{26}O$ requires: C, 81·1; H, 11·71%). The second fraction (2·4 g) having b.p. 127°/2·5 mm solidified overnight to a colourless waxy solid, m.p. 81–86°. A third fraction (10·3 g) was obtained from the residue (which had crystallized overnight) by taking it up in ethanol and distilling it separately to give a white waxy solid, b.p. 142–145°/5 mm.

Isolation of the solid alcohol (A)

The second fraction (2·4 g) dissolved in the minimum amount of pet. ether (3 ml) was cooled to 0° to yield a white crystalline solid (0·65 g; m.p. 100–105°); two more recrystallizations furnished shining white silky needles, m.p. 107–108° (constant). The third fraction (9·85 g) on similar treatment yielded colourless crystals (2·45 g) whose m.p. and mixed m.p. with the above alcohol remained the same. It had $[\alpha]_D$ +53·3° (c = 4·8%, ethanol) (Found: C, 80·35; H, 11·45. $C_{15}H_{26}O$ requires: C, 81·08; H, 11·71%).

* Supplied by the Emil Greiner Co., New York.

The 3,5-*dinitrobenzoate* was prepared from the solid alcohol (A) (220 mg), 3,5-dinitrobenzoyl chloride (230 mg), dry benzene (5 ml) and dry pyridine (0·1 ml) at room temp (60 hr). The crude product (300 mg; m.p. 134–139°) after two recrystallizations from benzene–petroleum ether mixture (1 : 1) gave colourless prismatic needles, m.p. 144–145° (Found: N, 6·50. $C_{22}H_{28}O_6N_2$ requires: N, 6·73%).

Oxidation to the ketone. The complex[5] prepared from chromium trioxide (1·5 g; 0·015 M) in dry pyridine (15 ml) was treated with a solution of the solid alcohol (A, 1·1 g; 0·005 M) in dry pyridine (11 ml) and kept at room temp (24–26°) for 42 hr. The reaction mixture was diluted with water (100 ml) and the product steam-distilled; the distillate (500 ml) was extracted with pet. ether (30 ml × 5), washed neutral with water, dried and the solvent removed. Distillation of the residue gave a colourless liquid, b.p. 120–125°/3 mm, yield 0·8 g (73%).

The *semicarbazone* prepared by the sodium acetate method and recrystallized from ethanol, was obtained as white crystals, m.p. 211–213°, mixed m.p. with the reactive ketone semicarbazone (*vide infra*) was undepressed.

Oxidation of the liquid alcohol mixture and separation of the ketones

A typical experiment was as follows: To a solution of the alcohol (10·2 g) in glacial acetic acid (40 ml) was added dropwise (35 min) a solution of chromic acid (7·5 g) in 80% acetic acid (100 ml), under stirring, at room temp. The exothermic reaction was controlled by external cooling so that the reaction temp did not exceed 40–50°. The stirring was continued for another 2 hr and the reaction mixture left at room temp (64 hr); diluted with water (500 ml), extracted with pet. ether (30 ml × 5), washed with bicarbonate solution and with water till neutral, dried and the solvent flashed off through a column. Distillation of the residue gave a colourless mobile liquid, b.p. 111–112°/1·5 mm, yield 8·65 g (85·6%).

Isolation of the reactive ketone as semicarbazone. The above oxidation product (8·65 g) was treated with a saturated solution of semicarbazide hydrochloride (6·0 g) and fused sodium acetate (5·6 g) in water (25 ml). Ethanol (50 ml) was added to obtain a clear solution and soon after, the white crystalline derivatives separated. After 4 days this was filtered, washed with water and dried; m.p. 195–200° (dec), yield 5·52 g (50·5%). Three recrystallizations of the crude derivative (2 g) from aqueous ethanol gave shining white crystals (0·3 g), m.p. 215–216° (dec) (Found: C, 69·29; H, 9·75; N, 15·12. $C_{16}H_{27}ON_3$ requires: C, 69·31; H, 9·75; N, 15·16%).

The 2,4-*dinitrophenylhydrazone* was prepared via the semicarbazone as follows. To a solution of 2,4-dinitrophenylhydrazine (200 mg), conc sulphuric acid (1 ml), water (3 ml) and ethanol (10 ml) was added the pure semicarbazone (300 mg). After keeping at room temp overnight, the orange precipitate was filtered (300 mg; m.p. 130–133°) and twice recrystallized from aqueous ethanol to obtain orange needles m.p. 156–158° (Found: N, 13·81. $C_{21}H_{29}O_4N_4$ requires: N, 14%).

Isolation of the unreactive portion from mother liquor. The first mother liquor was diluted with water till turbid, warmed on the water bath till the solution was clear and left aside at room temp for 10 days. After filtering off a small quantity (250 mg; m.p. 195–199°) of the precipitated solid, the filtrate was steam-distilled; the distillate (ca. 800 ml) was extracted with pet. ether (30 ml × 4), washed with brine till neutral, dried and the residue, after removal of solvent, was distilled to obtain a colourless mobile liquid, b.p. 110–112°/1·5 mm, n_D^{24} 1·4995, yield 2·5 g (29% of the ketone mixture). In another experiment the unreactive portion was worked up by ether extraction.

Reactive ketone

Regeneration from semicarbazone. The semicarbazone (18·55 g; m.p. 210–214°) and a saturated solution of oxalic acid (45 g in 120 ml of water) were mixed and directly steam-distilled. The distillate (1300 ml) was extracted with pet. ether (30 ml × 9) and worked up as usual to yield a colourless mobile liquid, b.p. 129°/4 mm, n_D^{27} 1·4980, d_4^{27} 0·9902, M_D 65·14 (Calc. 64·9), $[\alpha]_D$ +36·1° (*c* = 5%; ethanol), yield 13·45 g (91%) (Found: C, 81·61; H, 10·89. $C_{15}H_{24}O$ requires: C, 81·83; H, 10·91%).

Reduction to the solid alcohol (A)

(i) *With lithium aluminium hydride.* To a slurry of the hydride (100 mg) in dry ether (40 ml) was added, with stirring, a solution of the ketone (550 mg) in the same solvent (15 ml) at room temp (29°) and stirred for 2 hr. The excess of the hydride was decomposed by adding ice-water and the complex

[5] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953).

hydrolysed with ice-cold dil sulphuric acid (10 ml). Usual work up gave the crude alcohol as a colourless solid (520 mg; m.p. 86–94°) which was thrice recrystallized from pet. ether to yield silky white needles, m.p. 105–106°, undepressed on admixture with the solid alcohol (A).

The 3,5-*dinitrobenzoate* of the crude alcohol (m.p. 86–94°), prepared in the usual way and recrystallized thrice from benzene–pet. ether at 0° deposited colourless crystals, m.p. 137–139°; mixed m.p. with the derivative of the solid alcohol (A) showed no depression.

(ii) *With sodium-n-propanol.* To a solution of the ketone (500 mg) in dry n-propanol (30 ml) kept on the steam-bath, pieces of sodium (1·5 g) were added in 4 lots during 40 min; after another 3 hr the excess of propanol was removed under suction; water (200 ml) was added, extracted with pet. ether (20 ml × 3), washed with water, dried and the solvent removed. The residue (520 mg) solidified slowly which had m.p. 80–84°; on admixture with the solid alcohol (A) the m.p. was raised to 91–97°.

Separation of the solid alcohol (B) from longicamphor

The unreactive portion (11·06 g) in dry pet. ether (20 ml) was chromatographed over alumina (Basic/I; 140 g; 34·5 × 2·4 cm). Elution with pet. ether (520 ml) gave a liquid (longicamphor; 8·52 g) and further washings with ether (280 ml) yielded the crystalline solid alcohol (B) (2·36 g), m.p. 82–90°. Repeated recrystallizations from n-hexane at 0° gave fine silky white clusters of needles, m.p. 92–94°, $[\alpha]_D$ −6·1° (*c* = 4·1%; ethanol) (Found: C, 81·47; H, 11·73. $C_{15}H_{26}O$ requires: C, 81·08; H, 11·71%). Mixed m.p. with the solid alcohol (A) was depressed to 62–75° and with authentic longiborneol was lowered to 62–74°.

Longicamphor

The above pet. ether eluterate was fractionated to give a colourless mobile liquid, b.p. 100°/0·6 mm, n_D^{26} 1·4990, d_4^{26} 0·9949, M_D 64·95 (calc. 64·9), $[\alpha]_D$ +18·8° (*c* = 5·3%; ethanol) (yield: 24% of the oxidation mixture; ca. 6% based on longifolene) (Found: C, 81·44; H, 10·90. $C_{15}H_{26}O$ requires: C, 81·83; H, 10·91%). Naffa and Ourisson[2] report b.p. 160–165°/15 mm, n_D^{20} 1·4989, $[\alpha]_D$ +22° (*c* = 5·8%; ethanol).

Reduction to longiborneol. To a solution of the ketone (500 mg) in dry n-propanol (30 ml) were added sodium pieces (1 g) and kept at room temp (20 min); another lot of sodium (500 mg) was then added and refluxed on the water bath (2 hr) and worked up as described previously to give a pale yellow solid (500 mg; m.p. 82–100°) which was chromatographed over alumina (6 g). The main fraction (m.p. 100–105°) eluted by pet. ether was sublimed on the steam-bath under vacuum (water-pump) to obtain glistening white crystals, m.p. 105–107° (Found: C, 81·11; H, 11·76. $C_{15}H_{26}O$ requires: C, 81·08; H, 11·71%). Mixed m.p. with an authentic sample of longiborneol showed no depression.

The 3,5-*dinitrobenzoate* prepared in the usual fashion and recrystallized from benzene–pet. ether furnished colourless needles, m.p. 155–156° (Found: N, 6·64. $C_{22}H_{28}O_6N_2$ requires: N, 6·73%).

Isolongifolene

Isolongifolene (235 g) having α_D −77° was subjected to precise fractionation in the "Emil Greiner's column and in all, 24 fractions were collected, the course of fractionation being followed by noting the b.p., n_D and M_D for each cut (ca. 10 ml). Fractions 5 to 22 having b.p., 112 to 114°, α_D −80·4 to −83·8° and $n_D^{32·5}$ 1·4980 to 1·4990 were mixed up (164·3 g) and distilled over sodium to yield isolongifolene as a colourless mobile liquid, b.p. 82–83°/0·4 mm, $n_D^{26·5}$ 1·4980, $d_4^{26·5}$ 0·9292, M_D 64·46 (calcd. for $C_{15}H_{24}F_1$ 64·43), α_D −82·2° (homogeneous), $[\alpha]_D$ −78·1° (*c* = 5·5%; ethanol) (Found: C, 88·08; H, 11·81. $C_{15}H_{24}$ requires: C, 88·16; H, 11·84%).

Isolongifolane. Hydrogenation of isolongifolene failed to take place over Adam's catalyst in alcoholic solution but in acetic acid it readily absorbed 1·05 mole of hydrogen at room temp and press to yield the saturated dihydro compound. Isolongifolane, thus obtained, was a colourless mobile liquid, b.p. 84°/0·4 mm, $n_D^{26·5}$ 1·4930, $d_4^{26·5}$ 0·9272, M_D 64·57 (Calc. 64·87), α_D +4° (homogeneous) (Found: C, 87·33; H, 12·56. $C_{15}H_{28}$ requires: C, 87·38; H, 12·62%). Infra-red absorption:* 1344, 1331, 1316(st), 1293(st), 1274, 1240(st), 1200, 1172, 1160, 1127(st), 1103, 1070, 1060, 1030, 958(st), 944, 925, 907, 887, 870(st), 840 and 777 cm^{-1}.

Longifolane. Longifolene (2·37 g) on catalytic reduction over Adam's catalyst (50 mg) readily absorbed 1·06 moles of hydrogen at room temp and press during 2½ hr. Longifolane, thus prepared,

had b.p. 118°/4 mm, n_D^{26} 1·4942; negative tetranitromethane test. Infra-red absorption:* 1307, 1284, 1228, 1216, 1203, 1187, 1160, 1140(st), 1122(st), 1090(st), 1055(st), 1018(st), 982(st), 957(st), 944, 878(st), 861, 840, 810 and 768 cm^{-1}.

Vapour phase chromatography of isolongifolene was carried out on a Perkin–Elmer Vapor Fractometer, model 154 B. A 2-meter "Siliconecelite" column, at 225° with a column pressure of 28 lb/in² and a flow rate of 5·0, was employed. Helium was used as the carrier gas and a 0·002 ml sample was injected. This analysis was done at the Noyes Laboratories, University of Illinois, Urbana and the authors wish to express their sincere thanks to Prof. E. J. Corey for these facilities.

* Determined on a Perkin–Elmer double-beam instrument.

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DIARYLIODONIUM SALTS—XII

THE PHENYLATION OF DIMEDONE, DIBENZOYLMETHANE AND TRIBENZOYLMETHANE[1-4]

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(*Received* 23 *February* 1959)

Abstract—Diphenyliodonium salts in t-butyl alcohol have converted the anions of dimedone, dibenzoylmethane and tribenzoylmethane to C-phenyl, C, C-diphenyl, O-phenyl and O, C-diphenyl derivatives, the structures of which have been proved by degradation and synthesis. Reactions of dimedone in methanol or ethanol gave mainly products arising from dehydrogenation of the solvent.

INTRODUCTION

PAPERS of this past year have dealt with the synthesis[6,7] of diphenyliodonium salts, their reactions with nucleophilic reagents[3,8-10] (including their copper-catalyzed reactions[7,9-11]) their electroreduction,[11,12] their use in the synthesis of diphenylenes,[7a] terphenyls[7b] and organometallic compounds[13] and the synthesis and properties of iodonium salts from thiophene.[13b]

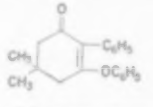
In the present paper there are reported the reactions of the carbanions from

[1] This paper is taken from the dissertations of P. S. Forgione and of M. D. Yudis, submitted in partial fulfillment of the requirements of the degree of Doctor of Philosophy at the Polytechnic Institute of Brooklyn.

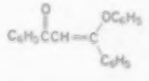
[2] The phenylation of dimedone by the present authors was reported at the New York Meeting of the Amer. Chem. Soc. Sept. (1957) (Abstracts of Papers, p. 36P).

[3] While this manuscript was in preparation there appeared an independent report of the phenylation of dimedone by Russian workers: O. Neilands, G. Vanags and E. Gudriniece, *J. Gen. Chem. U.S.S.R.* **28**, 1201 (1958); *Chem. Abstr.* **52**, 19988 (1958).

[4] For brevity, the trivial name dimedone is used here in place of the systematic names 5, 5-dimethyl-1-cyclohexen-1-ol-3-one and 5, 5-dimethylcyclohexane-1, 3-dione but with their numbering systems. Phenyl ethers of the enolic forms of the ketones are named as O-phenyl derivatives; eg.,



O, 2 – diphenyldimedone



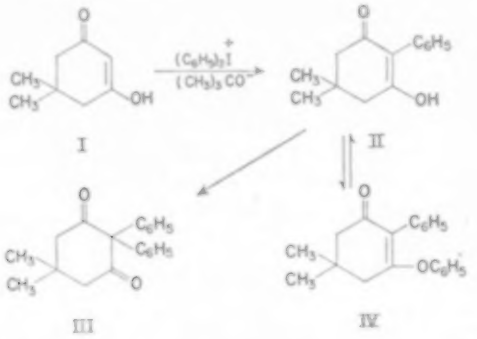
O – phenyldibenzoylmethane

[5a] Visiting Associate Professor, Yale University, 1958–1959.
[5b] Alfred P. Sloan Foundation Fellow, 1956–1959.
[5c] Alfred P. Sloan Foundation Fellow, 1959.
[6a] F. M. Beringer, R. A. Falk, I. Lillien, M. Karniol, G. Masullo, M. Mausner and E. Sommer, *J. Amer. Chem. Soc.* **81**, 342 (1959); [b] F. M. Beringer and R. A. Falk, *Ibid.* **81**, 2997 (1959).
[7a] W. Baker, J. W. Boston and J. F. W. McOmie, *J. Chem. Soc.* 2658 (1958); [b] R. C. Fuson and R. L. Albright, *J. Amer. Chem. Soc.* **81**, 487 (1959).
[8] F. M. Beringer, E. M. Gindler, M. Rapoport and R. J. Taylor, *J. Amer. Chem. Soc.* **81**, 351 (1959).
[9] M. C. Caserio, D. L. Glusker and J. D. Roberts, *J. Amer. Chem. Soc.* **81**, 336 (1959).
[10] F. M. Beringer and M. Mausner, *J. Amer. Chem. Soc.* **80**, 4535 (1958).
[11] H. E. Bachofner, F. M. Beringer and L. Meites, *J. Amer. Chem. Soc.* **80**, 4269 (1958).
[12a] H. E. Bachofner, F. M. Beringer and L. Meites, *J. Amer. Chem. Soc.* **80**, 4274 (1958); [b] F. M. Beringer H. E. Bachofner, R. A. Falk and M. Leff, *J. Amer. Chem. Soc.* **80**, 4279 (1958).
[13] O. A. Reutov, O. A. Ptitsyna and H. Hung-Weng, *Dokl. Akad. Nauk SSSR* **122**, 825 (1958); O. A. Reutov, O. A. Ptitsyna and N. B. Stiazhkina, *Ibid.* **122**, 1032 (1958).

dimedone, dibenzoylmethane and tribenzoylmethane with the diphenyliodonium cation in t-butyl alcohol. The reactions of the carbanion from dimedone with both the diphenyliodonium and the 2-nitrodiphenyliodonium ions were also studied in methanol and ethanol (in which solvents quite different results were obtained).

The phenylation products from dimedone[2-4]

In t-butyl alcohol at reflux dimedone (I) was converted by sodium t-butoxide and diphenyliodonium chloride or tosylate into 2-phenyldimedone (II) and 2,2-diphenyldimedone (III), while at room temperature 0,2-diphenyldimedone (IV) was also obtained. In water 2,2-diphenyldimedone was obtained, but no monophenylated product could be isolated. It was shown that 2-phenyldimedone could be converted under the first conditions to 2,2-diphenyldimedone, while mild acid hydrolysis of 0,2-diphenyldimedone gave 2-phenyldimedone and phenol.



In Table 1 the results obtained in the present work in t-butyl alcohol or water are summarized and compared with those of Neilands *et al.*[3]

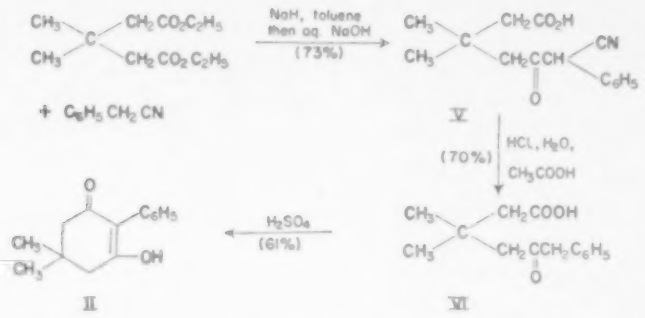
The structure of 2-phenyldimedone (II) was unequivocally established by its

TABLE 1. PHENYLATION PRODUCTS OF DIMEDONE AND 2-PHENYLDIMEDONE

Reaction conditions			Reagents		% Yield of products (based on diketone)		
Solvent	T (°C)	hr	Ketone	Anion	II	III	IV
1 : 1 w–d[a]	100°	2	I	Br	8·5	4	9
$(CH_3)_3COH$	83°	4	I	Cl	22	23	
$(CH_3)_3COH$[b]	83°	5	I	Cl	16	25	
$(CH_3)_3COH$	83°	4	I	TsO[c]	18	19	9
$(CH_3)_3COH$	25°	72	I	Cl	13	5	9
$(CH_3)_3COH$	83°	2	II	Cl		71	
H_2O	100°	4	I	Cl		14	

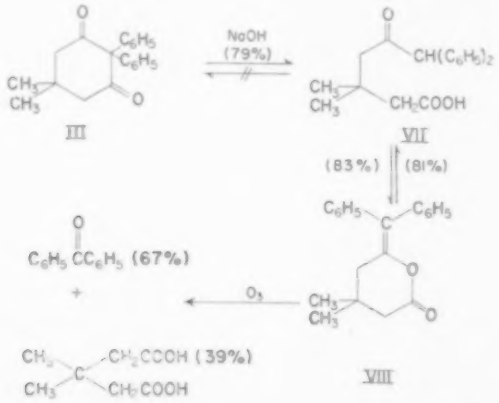
[a] The reaction in 1:1 water–dioxane was reported[3]; a very small amount of O-phenyldimedone was also obtained. The other reactions are those of the present work. [b]Reverse addition: anion of dimedone added slowly to diphenyliodonium chloride. [c]*p*-Toluenesulfonate (tosylate).

synthesis from ethyl β, β-dimethylglutarate.[14] The first step of the condensation gave in good yield the acid nitrile V, from which the nitrile group could be removed, also in good yield, by acid hydrolysis to VI. Ring closure to 2-phenyldimedone was best effected by the brief heating to 120° of keto acid VI in 72 per cent sulphuric acid.[15] The 2-phenyldimedone prepared by ring closure of VI was identical to that



obtained by the phenylation of dimedone. This established also the structure of 0,2-diphenyldimedone (IV). The direct reaction of V and its ethyl ester under these conditions gave high yields of crude product which unfortunately proved difficult to purify.

An attempt to prepare 2, 2-diphenyldimedone by a similar cyclization of keto acid (VII) with polyphosphoric acid[16] gave a six-membered cyclic enol lactone (VIII), whose structure was proved by ozonolysis to benzophenone and β,β-dimethylglutaric acid.



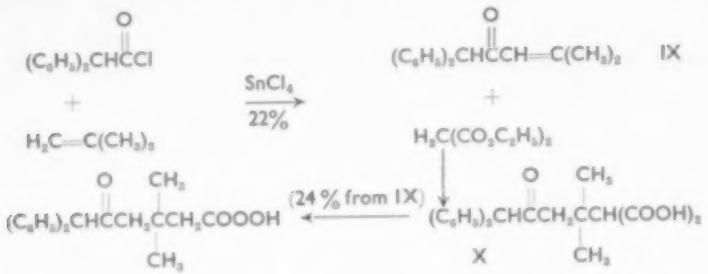
The structure of 2,2-diphenyldimedone was finally established by showing the

[14] The synthesis was patterned after the work of T. Henshall, W. E. Silbermann and J. G. Webster, *J. Amer. Chem. Soc.* **77**, 6656 (1955); W. E. Silbermann and T. Henshall, *Ibid.* **79**, 4107 (1957).

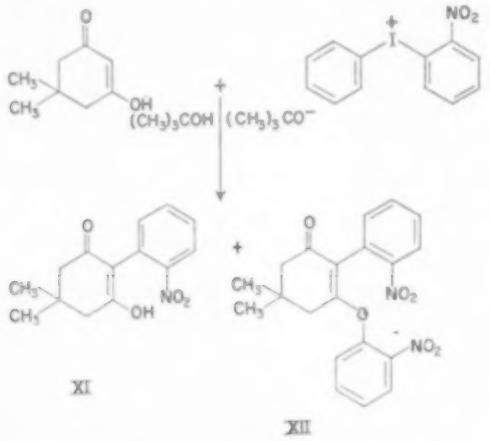
[15] 2-Phenyl-4,4-dimethylcyclohexane-1,3-dione has been prepared from ethyl 2,2-dimethyl-5-oxo-6-phenylhexanoate by condensation with sodium hydride in toluene: H. Born, R. Pappo and J. Szmaskocicz, *J. Chem. Soc.* 1779 (1953).

[16] P. D. Gardner and W. J. Horton, *J. Amer. Chem. Soc.* **75**, 4976 (1953) prepared the enol lactone of 2,3,4-trimethoxybenzosuber-5-one-6-acetic acid from β,β-dicarboxy-3,4,5-trimethoxyphenylcaproic acid with polyphosphoric acid. J. H. Helberger, S. Ulubay and H. Civelekoglu, *Liebigs Ann.* **561**, 215 (1949) prepared α-angelica lactone from levulinic acid in nearly quantitative yield using catalytic amounts of syrupy phosphoric acid.

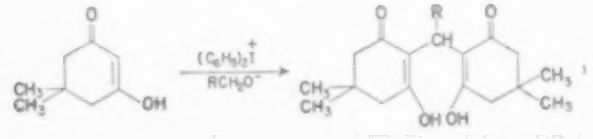
identity of keto acid VII obtained from III to that synthesized independently. The first step utilized the method of Colonge and Chambion.[17]



When 2-nitrodiphenyliodonium bromide replaced diphenyliodonium chloride in the reaction with dimedone in t-butyl alcohol, 2-(*o*-nitrophenyl)-dimedoue (XI) and 0,2-bis-(*o*-nitrophenyl)-dimedone (XII) were isolated but 2,2′-di-(*o*-nitrophenyl)-dimedone was not found. The structure of XI was confirmed by its periodate oxidation[18] to *o*-nitrobenzoic and β,β-dimethylglutaric acids, while the structure of XII was demonstrated by its hydrolysis with hydrobromic acid to XI.



The replacement of t-butyl alcohol by methanol or ethanol brought about a complete change in the nature of the main products. The reaction of 2-nitrodiphenyliodonium bromide in methanol produced 2,2-methylene-bis-dimedone (XIIIa) as the only isolable product in 66 per cent yield. With diphenyliodonium chloride in



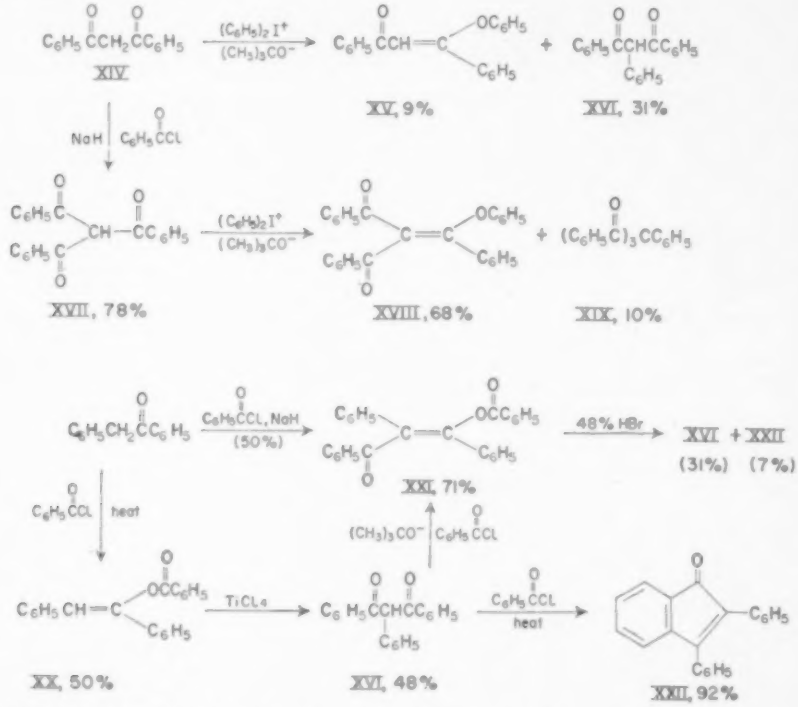
XIIIa, R=H; XIIIb, R=CH$_3$

[17] J. Colonge and J. Chambion, *C.R. Acad. Sci., Paris* **224**, 128 (1947).
[18] M. L. Wolfrom and J. M. Bobbitt, *J. Amer. Chem. Soc.* **78**, 2489 (1956).

ethanol a complex mixture was formed from which 2-phenyl- and 2,2-diphenyldimedone and 2,2′-ethylidene-bis-dimedone (XIIIb), as the corresponding octahydroxanthene,[19] were all isolated in low yields. In some manner, to be discussed in a later paper, the iodonium cation had apparently dehydrogenated alcohol to aldehyde, which then condensed with the dimedone.[19]

Phenylation products from di- and tribenzoylmethane[4]

The products of the reactions of the carbanions of di- and tribenzoylmethane with diphenyliodonium chloride in t-butyl alcohol are now shown with their alternative syntheses.[20]



On vigorous alkaline hydrolysis products XV and XVIII gave phenol, acetophenone and benzoic acid and are thus phenyl ethers. The isomeric products XVI and XIX under similar conditions gave desoxybenzoin and benzoic acid and are thus C-phenyl derivatives.[21]

The preceding reaction scheme includes two routes to phenyldibenzoylmethane (XVI) from desoxybenzoin: (a) the formation and rearrangement of enol benzoate XX in overall yield of about 25 per cent, and (b) the formation and hydrolysis of enol

[19] E. C. Horning and M. G. Horning, *J. Org. Chem.* **11**, 95 (1946).

[20] Di- and tribenzoylmethane and phenyldibenzoylmethane are conventionally represented in their non-enolic forms. The geometry of compounds XV, XX and XXI is not known.

[21] It has been reported that C-phenyltribenzoylmethane (XIX) was formed by the reaction of excess ethereal benzoyl chloride with the sodium salt of desoxybenzoin: J. Meisenheimer and K. Weibezahn, *Ber.* **54** 3195 (1921). That the product so prepared is, rather, the vinyl benzoate XXI is shown by a depression of m.p. with authentic XIX and by the presence in the infrared spectrum of ester carbonyl absorption (5·74 μ) and conjugated ketone absorption (6·0 μ).

benzoate XXI in overall yield of about 15 per cent. Neither is as attractive as the direct phenylation of dibenzoylmethane.

An attempt at direct C-benzoylation of phenyldibenzoylmethane by heating with benzoyl chloride gave instead the red dehydration product 2,3-diphenylindenone (XXII).

t-Butyl phenyl ether. When reactions were first run in t-butyl alcohol, it was thought that one product might be that of the t-butoxide ion with the diphenyliodonium cation, namely t-butyl phenyl ether.

$$(CH_3)_3CO^- + C_6H_5\overset{+}{I}C_6H_5 \rightarrow (CH_3)_3COC_6H_5 + C_6H_5I$$

It was found that the two ions reacted smoothly, but that direct separation of the products was difficult. However, catalytic hydrogenation of the mixture converted the iodobenzene to benzene and biphenyl and allowed isolation of t-butyl phenyl ether in 40 per cent overall yield.

This result is especially interesting in view of the recent failure of Scardiglia and Roberts[22] to produce this ether by addition of the t-butoxide ion to benzyne produced from bromobenzene with amide ion in liquid ammonia.

No t-butyl phenyl ether was found in runs with di- or triketones, however, presumably because the concentration of t-butoxide ion was so low.

DISCUSSION

The synthesis of compounds of the type C_6H_5CHYZ (where Y and Z are aryl or electron-attracting groups) might be accomplished in the following general sequences; each arrow may represent one or more preparative steps.

(I) $C_6H_5CH_3 \rightarrow C_6H_5CH_2Y \rightarrow C_6H_5CHYZ$
(II) C_6H_4 (benzyne) $+ H_2CYZ \rightarrow C_6H_5CHYZ$
(III) $C_6H_5X + HCYZ \rightarrow C_6H_5CHYZ + X$

Sequence I involves the conversion of toluene through mono-substituted and disubstituted compounds by a series of substitutions, condensations and alterations. A synthesis of phenylmalonic ester is an example.[23]

Sequence II is exemplified by the work of Levine and Leake[24] in which a carbanion is added to benzyne, and the ring of the adduct is protonated. An example is the phenylation of malonic ester (51 per cent yield).[24]

Sequence III involves the replacement of an aromatic substituent by a group HCYZ, which could be anionic, radical or cationic. In the present work, C_6H_5X is the diphenyliodonium cation and HCYZ is a carbanion derived from a diketone. In the following equation R may be hydrogen or an alkyl, aryl or acyl group.

$$C_6H_5\overset{+}{I}C_6H_5 + \overset{O}{\overset{\|}{\underset{-}{C}}}R(CR')_2 \rightarrow C_6H_5CR(\overset{O}{\overset{\|}{C}}R')_2 + C_6H_5I$$

The few cases studied so far show that phenylation of carbanions with iodonium salts has two problems well-known in alkylation: substitution on oxygen and disubstitution. Regarding the alkylation of ambident ions it has been stated: "the

[22] F. Scardiglia and J. D. Roberts, *Tetrahedron* **3**, 200 (1958).
[23] P. A. Levene and G. M. Meyer, *Organic Syntheses* Coll. Vol. II, p. 288. John Wiley, New York (1943).
[24] R. Levine, San Francisco meeting of the Amer. Chem. Soc., April (1958) (Abstracts of Papers, p. 9M); W. W. Leake and R. Levine, *Chem. & Ind.* 1160 (1955); *J. Amer. Chem. Soc.* **81**, 1169 (1959).

greater the S_N1 character of the transition state the greater is the preference for covalency formation with the atom of higher electronegativity and, conversely, the greater the S_N2 contribution to the transition state the greater the preference for covalency formation with the atom of lower electronegativity."[25] Of ambident ions previously studied with the iodonium salts,[26] most (nitrite, sulfite, sulfinate, cyanide and the anions from sulfonamides and from ethyl oxalacetate) have given products with the new covalency to the less electronegative atom; only phenoxide ions have formed products (ethers) through the more electronegative atoms.

With respect to disubstitution, in one case it was not observed (dibenzoylmethane), while in another (dimedone) both O,C- and C,C-disubstituted products were formed. With the latter diketone the relative amounts of monophenyl and diphenyl derivatives seemed to be relatively insensitive to the order of addition.

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It is planned to discuss the mechanisms of these reactions in forthcoming papers on reactions of iodonium salts with organometallic compounds and with carbanions from esters.

EXPERIMENTAL[27]

Starting materials. Dimedone was used as received from Eastman Organic Chemicals, while dibenzoylmethane[28] and the various iodonium salts were prepared according to published procedures. Phenylacetonitrile was redistilled before use. Ethyl β,β-dimethylglutarate was obtained by the esterification of β,β-dimethylglutaric acid prepared by the Guareschi synthesis from acetone and cyanoacetamide.[29] Diphenylacetyl chloride was prepared from diphenylacetic acid (obtained from Eastman Organic Chemicals) by the action of thionyl chloride. Absolute methanol and ethanol were used as received, while t-butyl alcohol was redistilled from sodium.

Tribenzoylmethane was made by a modification of the procedure of Abell[30] as follows. To a suspension of 12·0 g (0·5 mole) of sodium hydride in 2 l. of anhydrous ether, dibenzoylmethane (112 g, 0·5 mole) was added over 1 hr. After 3 hr at room temp. the stirred mixture containing a gel-like suspension was treated with 70 g (0·5 mole) of benzoyl chloride in 50 ml anhydrous ether. As the addition progressed, the suspension could be stirred more easily. Twelve hours later there were added 10 ml ethanol, 300 ml water and, finally, 100 ml 6 N HCl. The solid precipitate was collected, washed with water and dried to give 156 g (0·39 mole 78%) of tribenzoylmethane, m.p. 225–226°; reported[30] m.p. 224–226°. No other product was obtained from the ether layer. Several crystallizations from acetonitrile raised the m.p. to 237–238°; λ_{max} 250 and 330 mμ, ε 26,700 and 6500.

(Found: C, 80·62; H, 4·95. Calc. for $C_{22}H_{16}O_3$: C, 80·47; H, 4·91%).

t-Butyl Phenyl Ether

Diphenyliodonium chloride with potassium t-butoxide in t-butyl alcohol

Diphenyliodonium chloride (270 g, 0·854 mole) was added over 30 min to a solution of 35·1 g (0·9 g atom) of potassium in 1500 ml t-butyl alcohol. The temperature was allowed to reach but not exceed 60°. After 6 hr at room temp. the reaction mixture was filtered to give 56 g (0·76 mole) potassium chloride.

The filtrate was concentrated to 300 ml by distillation of t-butyl alcohol. To the residue a solution

[25] N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, *J. Amer. Chem. Soc.* **77**, 6269 (1955).
[26] F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler and C. C. Lumpkin, *J. Amer. Chem. Soc.* **75**, 2708 (1953); F. M. Beringer and E. M. Gindler, *J. Amer. Chem. Soc.* **77**, 3203 (1955).
[27] Analyses were performed by the Schwarzkopf Micro-analytical Laboratories, Woodside, New York, by Dr. K. Ritter, Basel, Switzerland, and by the analytical laboratories of the Schering Corp. Melting points were corrected. Ultraviolet spectra were obtained in methanol and alkaline methanol where noted. Neutralization equivalents and dissociation constants were determined potentiometrically in 50% (v/v) aqueous ethanol.
[28] C. F. H. Allen, R. D. Abell and J. B. Normington, *Organic Syntheses* (2nd Ed.) Coll. Vol. I, p. 205. John Wiley, New York (1941).
[29] F. B. Thole and J. F. Thorpe, *J. Chem. Soc.* **99**, 422 (1911).
[30] R. D. Abell, *J. Chem. Soc.* **101**, 998 (1912).

of 60 g KOH in 20 ml water and 100 ml methanol was added. This solution was treated with hydrogen at 2–3 atmospheres press. in the presence of 10 g 5% palladium on calcium carbonate until uptake ceased. After removal of the catalyst, the reaction mixture was diluted with 1 l. water and extracted with ether. Distillation gave 51 g (0·34 mole, 40%) of *t-butyl phenyl ether*, b.p. 84–85° at 19 mm n_D^{27} 1·4905.

(Found: C, 79·74; H, 9·31; Calc. for $C_{10}H_{14}O$: C, 79·94; H, 9·38%).

Constants previously reported for t-butyl phenyl ether are the boiling point[21] (80°/20 mm) and the refractive index[22] (n_D^{20} 1·4880).

Isomerization of t-butyl phenyl ether to 4-t-butylphenol

Addition with cooling of 1·0 g anhydrous titanium tetrachloride to 2·0 g (13·3 mmoles) t-butyl phenyl ether gave a solution which soon turned red and solidified. After 5 min 115 ml water containing 1·5 g NaOH was added, giving a white precipitate of hydrated titanium dioxide. This was collected and washed with 10 ml 0·1 N NaOH. The aqueous solutions were combined and made weakly acid with HCl. The precipitate was collected and recrystallized from water to give 1·4 g (9·2 m moles, 60%) of 4-t-butylphenol, m.p. 98–99°, undepressed by admixture with an authentic sample.

Reference Compounds Related to Dimedone

(a) 2-*Phenyldimedone by ring closure*

3,3-*Dimethyl-5-oxo-6-cyano-6-phenylhexanoic acid* (V). To 95 g of a 25% suspension of sodium hydride (0·99 mole) in mineral oil was added 55·2 g (0·47 mole) phenylacetonitrile in 300 ml dry toluene and the mixture was stirred for 12 hr at room temp. After 102 g ethyl β,β-dimethylglutarate in 100 ml toluene was slowly added (exothermic reaction), the suspension was heated at 60° for 6 hr with vigorous stirring. Material which separated from the toluene solution was repeatedly extracted with benzene and then discarded. The condensation product (acidic due to the α-cyano-ketone group) was extracted from the combined organic phase with 1 N NaOH and saponified by heating for 3 hr on the steam bath. The aqueous solution was acidified, and the ethereal extract of the acid was washed with water, decolorized with charcoal and dried. Evaporation of the ether gave 90·2 g (0·347 mole, 73%) crude 3,3-*dimethyl-5-oxo-6-cyano-6-phenylhexanoic acid* (V), m.p. 100–104°. Recrystallization from acetic acid–hexane and from benzene gave material of m.p. 108–110°; λ_{max} 270 mμ, ε 14,300; $\lambda_{max}^{0\cdot1N\ NaOH}$ 254 and 305 mμ, ε 8900 and 17,300.

(Found: C, 70·35; H, 6·76; N, 5·29; neut. equiv. 262 ± 2. Calc. for $C_{15}H_{17}O_3N$: C, 69·47; H, 6·61; N, 5·40%; neut. equiv., 259·3.)

The ethyl ester of V was prepared by refluxing the acid with ethanol in benzene containing 1% conc. H_2SO_4. Distillation gave as the main product the ethyl ester of V, b.p. 153–155°/0·3 mm, d_4^{24} 1·084, n_D^{27} 1·5304; λ_{max} 266 mμ, ε12,200; $\lambda_{max}^{0\cdot1N\ NaOH}$ 254 and 305 mμ, ε 9070 and 17,400.

(Found: C, 70·87; H, 7·27; Calc. for $C_{17}H_{21}O_3N$: C, 71·05; H, 7·37%).

3,3-*Dimethyl-5-oxo-6-phenylhexanoic acid* (VI). A 3 : 1 : 1 solution (260 ml) acetic acid, conc. HCl and water containing 21·3 g (82 mmoles) of cyanoacid V was boiled for 25 hr. After removal of solvent the residue was shaken with water and ether, giving 2·4 g of crude insoluble material, which was removed and crystallized from ethanol–water to give 1·48 g (6·84 mmoles, 8·3%) of *2-phenyldimedone* (II), m.p. 195–197°; mixed m.p. with material from dimedone and diphenyliodonium chloride 196–197°; infrared spectra were superposable.

The ethereal extract from which the solid had been removed was concentrated to give 18·2 g of a yellow oil, whose infrared spectrum showed no nitrile absorption. (A run of 18 hr indicated about 10% nitrile absorption in the crude product.) Vacuum distillation gave 13·4 g (57·2 mmoles, 70%) of *ketoacid* VI, of b.p. 139–141°/0·1 mm, as a light yellow oil, n_D^{24} 1·527.

(Found: C, 71·59; H, 7·58; neut. equiv. 232 ± 2. Calc. for $C_{14}H_{18}O_3$: C, 71·76; H, 7·74%; neut. equiv. 234·3).

The ethyl ester of VI, prepared as described for the ester of V, was distilled at 153–157°/4 mm, d_4^{25} 1·028, n_D^{20} 1·492.

[21] D. R. Stevenson, *J. Org. Chem.* **20**, 1232 (1955).
[22] W. T. Olson, H. F. Hipshen, C. M. Buess, I. A. Goodman, I. Hart, J. H. Lamneck and L. C. Gibbons, *J. Amer. Chem. Soc.* **69**, 2451 (1947).

(Found: C, 72·86; H, 8·42; Calc. for $C_{16}H_{22}O_3$: C, 73·24; H, 8·46%).

Cyclization of 3,3-*dimethyl*-5-*oxo*-6-*phenylhexanoic acid* (VI) *to* 2-*phenyldimedone* (II). A preliminary cyclization[14] of 5·41 g ketoacid VI in 55 ml 72% by weight H_2SO_4 was run at 120°. Aliquots (10 ml) were poured into ice water, and the products were filtered and dried.

Minutes	% Yield	M.p.
25	86	187–191°
75	77	182–187°
110	71	179–186°

On a preparative scale, 5·87 g (25 mmoles) ketoacid VI in 60 ml 72% H_2SO_4 was heated at 120° for 20 min, cooled and poured into ice water. The solids were recrystallized from aqueous ethanol and from ethyl acetate to give 3·3 g (15·2 mmoles, 61%) of 2-*phenyldimedone* (II), m.p. 197–198°; mixed m.p. with material from the reaction of dimedone with diphenyliodonium chloride, 197–198°; the infrared spectra were superposable.

The cyclization was attempted with cyanoacid V and its ester under similar conditions. Maximum yield of crude product (81%) was obtained after 2·7 hr, but the m.p. was broad and low, 156–174°, and only a small quantity of pure 2-phenyldimedone could be isolated after a number of crystallizations.

(b) *Synthesis of* 3,3-*dimethyl*-5-*oxo*-6,6-*diphenylhexanoic acid* (VII), *a cleavage product of* 2,2-*diphenyldimedone and its attempted ring closure*

Benzhydryl isobutenyl ketone (IX). To a solution of 138 g (0·61 mole) of diphenylacetyl chloride and 50·5 g (0·9 mole) of isobutylene in 700 ml carbon disulfide protected from moisture and cooled to −5°, there was added over 15 min 22 g (85 mmoles) of stannic chloride from a freshly opened bottle. The mixture was stirred for 4 hr at −5°, brought slowly to room temp. and stirred overnight.

The reaction mixture was treated with 600 ml 1 : 1 HCl, the phases were separated, and the aqueous phase was extracted three times with carbon disulfide. The carbon disulfide phase and extracts were combined, washed with aqueous potassium carbonate and with water, dried and concentrated to a dark brown oil. This residue was heated with 300 ml N,N-dimethylaniline for 2 hr at 180°. The cooled mixture was poured into 600 ml 1 : 1 HCl and extracted with three 300 ml portions ether. The ether extract was washed, dried and distilled to give 58 g crude product, b.p. 160–177°/3 mm. This was crystallized twice from ethanol to give 32·5 g (13·0 mmoles, 22%) *benzhydryl isobutenyl ketone* (IX), m.p. 75–76°, λ_{max} 245 mμ, ε 16,050.

(Found: C, 86·67; H, 7·30; Calc. for $C_{18}H_{18}O$: C, 86·36; H, 7·25%).

The 2,4-*dinitrophenylhydrazone of* IX, formed in the usual way and recrystallized from ethanol, melted at 148–149°.

(Found: N, 12·97. Calc. for $C_{24}H_{22}O_4N_4$: N, 13·02%).

A duplicate run yielded 19% of the desired unsaturated ketone IX. However, when the above procedure was varied in that 130 g (0·5 mole) stannic chloride was added to 115 g (0·5 mole) diphenylacetyl chloride and 56 g (1·0 mole) isobutylene in carbon disulfide at −5°, vacuum distillation of the crude product after treatment with dimethylaniline gave 41 g of a light yellow oil, b.p. 177–197°/4 mm, which gave no solid material after repeated attempts at crystallization. The infrared spectrum indicated phenyl, methyl and ketonic (saturated and unsaturated) absorption, suggesting a mixture of the desired unsaturated ketone IX with 1-phenyl-2-oxo-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene. This material was not further investigated.

1,1-*Dimethyl*-3-*oxo*-4,4-*diphenylbutylmalonic acid* (X). Equimolar quantities (53 mmoles) of benzhydryl isobutenyl ketone and diethyl sodiomalonate were boiled in ethanol for 5 hr. After saponification with KOH and an attempted decarboxylation with a small excess (20 mmoles) HCl, the usual treatment afforded 11·8 g (44 mmoles) crude recovered ketone and 2·54 g (7·2 mmoles) 1,1-*dimethyl*-3-*oxo*-4,4-*diphenylbutylmalonic acid* (X) m.p. 147–148° (with gas evolution) after crystallization from aqueous ethanol and from benzene.

(Found: C, 71·03; H, 6·12; neut. equiv. 352 ± 3; two breaks in titration curve typical of malonic acids. Calc. for $C_{21}H_{22}O_5$: C, 71·17; H, 6·26%; neut. equiv., 354·4).

3,3-Dimethyl-5-oxo-6,6-diphenylhexanoic acid (VII). A solution of 1·56 g (68 mg atom) of sodium, 10·9 g (68 mmoles) of diethyl malonate and 14·75 g (59 mmoles) of benzhydryl isobutenyl ketone in 125 ml ethanol was boiled under reflux for 25 hr. After a solution of 4·6 g KOH in 125 ml water had been added and 125 g ethanol–water had been removed by distillation, the solution was refluxed for 6 hr. The cooled solution was extracted with ether both before and after acidification; the latter extract on evaporation gave 11·0 g of a light yellow oil which did not crystallize. A part of this (8·85 g) in 100 ml acetic acid, 50 ml conc. HCl and 50 ml water was refluxed for 12 hr under nitrogen. Concentration of this solution, followed by extraction with ether and evaporation gave 4·47 g (14·4 mmoles, 30%) of *3,3-dimethyl-5-oxo-6,6-diphenylhexanoic acid* (VII), m.p. 96–99°. One crystallization from ligroin and one from aqueous methanol gave material of m.p. 103–103·5°; mixed m.p. 102–103° with material obtained from the cleavage of 2,2-diphenyldimedone. The infrared spectra of the acid obtained from these two sources were identical.

Attempted ring closure of VII *to 2,2-diphenyldimedone* (III)

Formation of β,β-dimethyl-δ-benzyhdrylidene-δ-valerolactone (VIII). To a solution of 3·10 g (10 mmoles) acid VII in 10 ml acetic acid was added 60 g polyphosphoric acid, and the mixture was shaken by hand with intermittent cooling to give a uniform, viscous solution, which was then heated at 55–60° for 1 hr. The reaction mixture was poured onto ice and gave a yellow oil which solidified after prolonged stirring. The solids were collected after the mixture had stood overnight, washed with water, dried and crystallized from ethanol to give 2·41 g (8·3 mmoles, 83%) of *β, β-dimethyl-δ-benzhydrylidene-δ-valerolactone* (VIII), m.p. 128–130°. Recrystallization from ethanol raised the m.p. to 131–132°; λ_{max} 254 mμ, ε 16, 030.

(Found: C, 78·36; H, 7·53. Calc. for $C_{20}H_{20}O_2 \cdot C_2H_5OH$: C, 78·07; H, 7·74%).

The infrared spectrum had prominent bonds at 5·67 μ (lactone carbonyl), 6·00 μ (C═C—O) and 6·23, 6·33 μ (phenyl). The lactone rapidly took up bromine in carbon tetrachloride but only slowly decolorized potassium permanganate. A solution of 1·79 g (6·1 mmoles) of the lactone in 300 ml 2 : 1 water-dioxane, 0·05 molar with potassium carbonate, was heated at 100° for 1 hr. Acidification and the usual workup, including crystallization from aqueous ethanol, gave 1·53 g (4·9 mmoles, 81%) of starting material acid VII, m.p. 100–102°, no depression on admixture with acid from the cleavage of 2,2-diphenyldimedone.

Ozonolysis of 585 mg (2·0 mmoles) of lactone VIII in 20 ml chloroform and 15 ml methanol at −10° gave 244 mg (1·34 mmoles, 67%) of benzophenone, m.p. 37–43°, and 125 mg (0·78 mmoles, 39%) of 3,3-dimethylglutaric acid, m.p. 101–102°; no depression on admixture with an authentic sample. The benzophenone gave a 2,4-dinitrophenylhydrazone of m.p. 236–238°; no depression on admixture with an authentic sample.

Reactions of Dimedone and 2-Phenyldimedone with Iodonium Salts

Dimedone with diphenyliodonium chloride and tosylate in t-butyl alcohol at reflux temperature. Dimedone (28·4 g, 202 mmoles) and after a few minutes diphenyliodonium chloride (64 g, 202 mmoles) were added to 1 l. t-butyl alcohol in which 4·6 g (200 mg atoms) sodium had been dissolved. The stirred suspension was boiled under nitrogen for 4 hr. The reaction mixture rapidly turned a deep yellow color at reflux temp., then slowly became lighter; at the end of the reaction the color was only slightly yellow. After steam distillation to remove iodobenzene (whose infrared spectrum showed the absence of benzene), the mixture was treated with a solution of 27·6 g potassium carbonate in 200 ml water and extracted thoroughly with ethyl acetate. The extract was washed with water, dried and concentrated to give 14·9 g crude product, which was crystallized from ethanol to give 13·3 g (45·5 mmoles, 23%) *2,2-diphenyldimedone* (III). Two additional crystallizations raised the m.p. to 181–182°.

(Found: C, 81·81; H, 7·17. Calc. for $C_{20}H_{20}O_2$: C, 82·15; H, 6·86%).

The extracted alkaline solution was acidified and chilled overnight. Solids (11·7 g) were collected and recrystallized from methanol to give 8·74 g *2-phenyldimedone* (II), m.p. 184–186°. Another 0·92 g of this product was obtained from the aqueous filtrate by extraction with ethyl acetate and recrystallization of the crude product from this solvent. There was thus obtained in all 9·66 g (44·6 mmoles, 22%) of *2-phenyldimedone* (II). The analytical sample which was crystallized from aqueous methanol and from ethyl acetate melted at 197–198°; λ_{max} 268 mμ, ε 11,560.

(Found: C, 77·84; H, 7·53; neut. equiv. 216; pK_a 6·51 ± 0·05. Calc. for $C_{14}H_{16}O_2$: C, 77·74; H, 7·46%; neut. equiv., 216·3).

The 2-phenyldimedone prepared above proved in all ways identical to that prepared by the ring closure of 3,3-dimethyl-5-oxo-6-phenylhexanoic acid (VI). There was no depression of m.p., and infrared spectra were superposable.

2,2-Diphenyldimedone was cleaved to the ketoacid VII as follows. To a solution of 11·7 g (40 mmoles) of 2,2-diphenyldimedone in 400 ml warm ethanol there was added rapidly 300 ml 15% NaOH aq, and the mixture was boiled under nitrogen for 2 hr. After removal of most of the ethanol by distillation and extraction of the remaining aqueous solution with ether, the aqueous phase was acidified and extracted with ether. Evaporation left an oily residue, which was crystallized from 1 : 1 methanol–water to give 9·88 g (31·7 mmoles, 79%) of *3,3-dimethyl-5-oxo-6,6-diphenylhexanoic acid*, VII, m.p. 101–102°. Crystallization from ligroin raised the m.p. to 102–103°.

(Found: C, 77·22; H, 6·82; neut. equiv. 311 ± 2. Calc. for $C_{20}H_{22}O_3$: C, 77·39; H, 7·14%; neut. equiv. 310·4).

There was no depression of m.p. on mixing VII prepared from III and that from IX. Also, the infrared spectra of the two samples were superposable.

A similar reaction with diphenyliodonium *p*-toluenesulfonate and dimedone in refluxing t-butyl alcohol for 4 hr yielded 16% of 2-phenyldimedone (II) and 19% of 2,2-diphenyldimedone (III). From the neutral fraction was obtained 9% 0,2-diphenyldimedone (IV) after chromatographic separation on alumina and recrystallization from aqueous ethanol.

Dimedone with diphenyliodonium chloride in t-butyl alcohol at reflux temperature; Reverse addition of reagents. Dimedone (14·0 g, 100 mmoles) was added to a solution of sodium (2·30 g, 100 mg atom) in 500 ml t-butyl alcohol. This solution was added dropwise under nitrogen over 5 hr to a boiling suspension of 31·8 g (100 mmoles) diphenyliodonium chloride in 500 ml t-butyl alcohol. Addition was sufficiently slow to prevent a yellow coloration of the suspension. A work-up similar to that described above gave 7·26 g (24·7 mmoles, 25%) *2,2-diphenyldimedone*, m.p. 179–180°, and 3·48 g (16·1 mmoles, 16%) of *2-phenyldimedone*, m.p. 193–195°.

Dimedone with diphenyliodonium chloride in t-butyl alcohol at room temperature; *0,2-diphenyldimedone* (IV). A suspension of 63·4 g (200 mmoles) of diphenyliodonium chloride in 1 l. of t-butyl alcohol in which 4·60 g (200 mg atom) of sodium and 28·0 g (200 mmoles) of dimedone had previously been dissolved was stirred for 72 hr at room temp. under nitrogen. After iodobenzene had been removed by steam distillation and after 43 g (300 mmoles) of potassium carbonate had been added, the mixture was extracted twice with ethyl acetate (extract A). The alkaline phase was now acidified and extracted with ethyl acetate, which yielded 17·2 g of yellow oily solids. Crystallization from ethanol gave 5·76 g (26·6 mmoles, 13%) of crude *2-phenyldimedone* (II) m.p. 171–178°. Infrared spectroscopy indicated that the residue was largely recovered dimedone.

The ethyl acetate solution (extract A) was washed with water, dried and evaporated to give 23·2 g of a dark, gummy residue, which was chromatographed on 550 g alumina. Elution with 3 : 1 hexane-ether gave 3·11 g crystalline 2, *2-diphenyldimedone* (III). Recrystallization from ethanol gave 2·88 g (9·9 mmoles, 5%) III, m.p. 180–182°; mixed m.p. 181–182° with 2,2-diphenyldimedone from the reaction under reflux. Elution with 3 : 1 and 1 : 1 hexane–ether gave 6·05 g of a light yellow oil, having a strong ultraviolet absorption maximum, λ_{max} 270 mμ, *E* 1% 433. Crystallization from aqueous ethanol gave 5·24 g (17·9 mmoles, 9%), 0, *2-diphenyldimedone* (IV), m.p. 73–75°. Recrystallization from ethanol gave IV of m.p. 77–78°, λ_{max} 271 mμ, ε 13,900.

(Found: C, 81·98; H, 7·11. Calc. for $C_{20}H_{20}O_2$: C, 82·15; H, 6·89%).

Further elution with ether and with methanol gave 4·38 g of a dark brown oil which solidified on standing but from which it was not possible to isolate crystalline material.

The structure of 0,2-diphenyldimedone (IV) was proved by its hydrolysis as follows. A solution of 2·92 g (10 mmoles) IV in 100 ml 2 : 1 methanol–water 1 N in hydrochloric acid was boiled for 1 hr. The mixture was concentrated to 50 ml, 100 ml water was added, and 2·03 g (9·40 mmoles, 94%) of *2-phenyldimedone*, m.p. 193–195°, was collected from the chilled solution. Crystallization from aqueous ethanol raised the m.p. to 196–197°. Ultraviolet and infrared spectra on this material were identical to those of material obtained by ring closure.

The filtrate was adjusted to pH 8·5 with sodium carbonate and extracted five times with ether, which on evaporation gave a pink oil with a phenolic odor. Bromination with a potassium tribromide

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solution gave 1·22 g (3·70 mmoles, 37%) of 2,4,6-tribromophenol, m.p. 92–93°; authentic sample, m.p. 96°; mixed m.p. 93–94°.

Dimedone with diphenyliodonium chloride in water. Diphenyliodonium chloride (31·7 g 100 mmoles) was treated with dimedone (14·0 g, 100 mmoles) previously dissolved in 400 ml water containing 100 mmoles of NaOH at reflux under nitrogen for 6 hr. After steam distillation to remove iodobenzene the usual work-up gave 6·9 g of a yellow neutral solid. Crystallization from ethanol gave 4·2 g (14·3 mmoles, 14%) of 2, 2-*diphenyldimedone*, m.p. 178–179°; mixed m.p. with material from a run in *t*-butyl alcohol, 178–180°. Some crude dimedone (8·35 g, 59·6 mmoles) was recovered. Infrared spectra showed the absence in the acidic fractions of any appreciable 2-phenyldimedone.

2-Phenyldimedone with diphenyliodonium chloride in t-butyl alcohol. A suspension of 19·5 g (61 mmoles) of diphenyliodonium chloride in 300 ml t-butyl alcohol in which 1·40 g (61 mg atoms) of sodium and 13·2 g (61 mmoles) of 2-phenyldimedone had been dissolved was boiled under nitrogen for 2 hr. The initial deep yellow-orange color lightened as the reaction proceeded. A work-up similar to that described above for dimedone under comparable conditions gave 14·5 g crude neutral product. Crystallization from ethanol gave in two crops 12·64 g (43·3 mmoles, 71%) of 2, 2-*diphenyldimedone* (III), m.p. 180–181°; mixed m.p. with a sample from dimedone, 181–182°.

Dimedone with 2-nitrodiphenyliodonium bromide in t-butyl alcohol. 2-Nitrodiphenyliodonium bromide (40·6 g, 100 mmoles) was added to a solution of 2·3 g (100 mg atoms) of sodium and 14·5 g (104 mmoles) of dimedone in 400 ml t-butyl alcohol. The suspension was stirred at 60° under nitrogen for 4 hr. A standard work-up gave 12·2 g crude acidic 2-(*o-nitrophenyl*)-*dimedone* (XI), m.p. 205–222°. Trituration with hot benzene yielded 7·61 g (29·1 mmoles, 29%) XI, which on crystallization from benzene–methanol gave light yellow platelets of m.p. 235–236°; λ_{max} 261, ϵ 16,100; $\lambda^{0.01\ N\ NaOH}_{max}$ 288 mμ, ϵ 22,100.

(Found: C, 64·35; H, 5·83; N, 5·27; neut. equiv. 263 ± 4; pK_a 5·83 ± 0·06. Calc. for $C_{14}H_{15}NO_4$: C, 64·35; H, 5·79; N, 5·36%; neut. equiv., 261).

The dark yellow oil obtained from the neutral fraction was chromatographed on alumina. Fractions eluted with benzene and crystallized from aqueous methanol afforded 2·97 g (7·8 mmoles, 8%) of 0,2-*bis*-(*o-nitrophenyl*)-*dimedone* (XII). m.p. 127–140°. Recrystallization from acetone–ether raised the m.p. to 140–141°; λ_{max} 254 mμ, ϵ 23,100, no change in λ_{max} in dilute base.

(Found: C, 63·06; H, 4·95; N, 7·54. Calc. for $C_{20}H_{18}O_6N_2$: C, 62·82; H, 4·74; N, 7·33%).

The structure of XII was demonstrated by hydrolysis as follows. A solution of 0·790 g (2·06 mmoles) XII in 25 ml acetic acid and 25 ml 48% HBr was heated 3 hr on the steam bath. The solution was concentrated to 10 ml and slowly diluted with water. From the chilled solution was collected 0·502 g (1·92 mmoles, 93%) of 2-(*o-nitrophenyl*)-*dimedone* (XI), m.p. 233–235°. The infrared spectrum was identical to that of XI obtained by arylation. An attempt at mild acid hydrolysis under the same conditions as was successful for 0,2-phenyldimedone (IV) yielded only unreacted starting material.

Dimedone with 2-nitrodiphenyliodonium bromide in methanol. 2-Nitrodiphenyliodonium bromide (41·1 g, 101 mmoles) was added to 450 ml methanol in which 2·3 g (100 mg atoms) of sodium and 14·6 g (104 mmoles) of dimedone had been dissolved. The stirred reaction mixture was boiled under gentle reflux for 13 hr. After removal of a small amount of insoluble material by filtration, the filtrate was cooled to −50° to give 4·38 g 2, 2-methylene-bis-dimedone (XIIIa). After concentration of the filtrate there was obtained additional crude XIIIa. This was crystallized from methanol–water to give 5·37 g material of m.p. 190–192°, for a total yield of 9·75 g (33·4 mmoles, 66%). Comparison of XIIIa with authentic material prepared from dimedone and formaldehyde showed that they had identical infrared spectra and no depression of melting point on mixing.

Reference Compounds Related to Di- and Tribenzoylmethane

1, 2-*Diphenylvinyl Benzoate* (XX). The procedure used was a modification of that recently described by Gogan *et al.*[33] A mixture of 14·0 g (0·714 mmoles) of desoxybenzoin and 35 ml benzoyl chloride was heated under a nitrogen atmosphere for 13 hr at 170°. The excess benzoyl chloride was evaporated at reduced pressure and the solution was cooled and taken up in ether, which was washed twice with potassium carbonate and then with water. Evaporation of the ether and addition of 200 ml ligroin gave on stirring a yellow-orange precipitate. Crystallization from

[33] F. Gogan, A. E. O'Brianin, E. M. Philbin, N. S. O'Connor, R. F. Timoney and T. S. Wheeler, *Tetrahedron* **3**, 143 (1958).

ethanol and treatment with charcoal gave white needles weighing 10·8 g (50%), m.p. 122–122·5° with softening at 120°; reported m.p. 119°.[33]

The infrared spectrum (KBr pellet) showed bands at 5·74 (ester C=O stretching vibration) and a band at 6·11 μ (C=C), while the ultraviolet spectrum exhibited maxima at 286 mμ, ϵ 34,600 and 226 mμ, ϵ 30,650.

(Found: C, 84·34; H, 5·37. Calc. for $C_{21}H_{16}O_2$: C, 84·00; H, 5·37%).

Phenyldibenzoylmethane (XVI). The rearrangement of enol benzoate XX using aluminum chloride[33] gave in our hands mostly tars and only a few percent of phenyldibenzoylmethane (XVI). A mixture of 1·0 g, (33 mmoles) 1,2-diphenylvinyl benzoate (XX) and 15 g titanium chloride were heated under reflux in a dry flask for 1·5 hr. At the end of this time the solution was poured into 44 ml conc. HCl and 40 g chopped ice. The solution was cooled to 5°, and the insoluble product was heated under reflux in 200 ml ethanol for 3 hr, treated with some charcoal and filtered. The solvent was evaporated on a steam bath, and the residue was treated with 5 ml methanol to give 0·55 g tan material, m.p. 135–138°. Crystallization from methanol gave 0·48 g (48%) phenyldibenzoylmethane (XVI) as tan needles, m.p. 146–147°. Repeated sublimation, taking the second half of each crop, gave white needles of product, m.p. 149–150°. A mixed melting point with the C-phenylated product of dibenzoylmethane, m.p. 149–150·5°, gave a m.p. 149–150°.

(Found: C, 84·16; H, 5·26. Calc. for $C_{21}H_{16}O_2$: C, 84·00; H, 5·37%).

2, 3-*Diphenylindenone* (XXII). A mixture of 0·51 g (17 mmoles) phenyldibenzoylmethane (XVI) and 10 ml benzoyl chloride was heated under an atmosphere of nitrogen for 15 hr at 160°. At the end of this time the excess of benzoyl chloride was evaporated at reduced pressure, and the oily residue was taken up in ligroin. This gave on standing 0·44 g (92%) dark red crystals, m.p. 151–152°. Further crystallization from ethanol gave red needles, m.p. 152–153°; reported m.p. 150–151°,[34] m.p. 153–155°[35].

(Found: C, 89·25; H, 5·16. Calc. for $C_{21}H_{14}O$: C, 89·33; H, 5·00%).

The phenylhydrazone derivative showed m.p. 175–176°; reported m.p. 175–176°.[35] The infrared spectrum (KBr pellet) of the ketone showed a strong band at 1710 cm^{-1} (C=O); reported[37] 1710 cm^{-1}. The ultraviolet spectrum showed a maximum at 258 mμ, ϵ 41,000.

2-*Benzoyl*-1, 2-*diphenylvinyl benzoate* (XXI). To 1500 ml anhydrous ether containing 16·8 g (0·7 mole) sodium hydride there was added with vigorous stirring over a period of 1 hr 137 g (0·7 mole) desoxybenzoin. The mixture was stirred for an additional hour, and then 98·4 g (0·7 mole) benzoyl chloride dissolved in 50 ml dry ether was added dropwise over a 2 hr period. The solution warmed up somewhat during the addition and turned from yellow to white when allowed to stir for 24 hr at room temp. At the end of this time 30 ml ethanol and 350 ml 1·2 N NaOH were added, giving a white solid, insoluble in both ether and water. Upon filtration 49·2 g material of m.p. 142–144° was isolated. Crystallization of this ester from ethanol gave 43·6 g of XXI, m.p. 152–153°, reported m.p. 152°.[31] The ethereal filtrate on evaporation gave 89 g (0·454 mole) of recovered desoxybenzoin. The yield of ester XXI based on unrecovered starting material was 50%. Admixture with phenyltribenzoylmethane (XIX) obtained from the phenylation of tribenzoylmethane gave a depression in melting point to 136–140°. The infrared spectrum (KBr pellet) showed bands at 5·74 μ (ester C=O), 6·0 μ (conjugated ketone); λ_{max} 233 mμ, ϵ 30,600.

(Found: C, 83·34; H, 5·19. Calc. for $C_{28}H_{20}O_2$: C, 83·15; H, 4·98%).

Phenyldibenzoylmethane (XVI, 1·0 g, 3·3 mmoles) was added with vigorous stirring to 70 ml dry t-butyl alcohol in which 76 mg (3·3 mg atoms) sodium had been dissolved. The mixture was stirred for 3 hr at 60°, forming a yellow sodium salt; 0·55 g (3·9 mmoles) benzoyl chloride was then added, and heating at 65° for 3 more hr gave a white suspension. After the alcohol was evaporated at reduced pressure, 400 ml water was added to the residue. The insoluble precipitate formed was collected, washed with cold water and crystallized from methanol–water to give 0·95 g (71%) enol benzoate XXI of m.p. 152–153°. A mixed melting point with authentic 2-benzoyl-1,2-diphenylvinyl benzoate (see above) gave no depression in m.p.; also the infrared spectra proved to be identical.

Hydrolysis of 2-*benzoyl*-1,2-*diphenylvinyl benzoate* (XXI). To a 50 ml flask containing 0·9 g (21 mmoles) XXI there was added 15 ml 48% HBr and, after 20 min of refluxing, 10 ml ethanol.

[34] H. Loewenbein and G. Ulich, *Ber.* **58**, 2662 (1925).
[35] R. Weiss and R. Sauerman, *Ber.* **58**, 2736 (1925).
[36] A. Orekjoff, *Bull. Soc. Chim. Fr.* (4) **25**, 598 (1919).
[37] E. D. Bergmann, G. Berthier, D. Ginsburg, Y. Hirschberg, D. Lavie, S. Pinchas, B. Pullman and A. Pullman, *Bull. Soc. Chim. Fr.* **18**, 661 (1951).

The solution was heated further for a total of 1·5 hr, concentrated by evaporative distillation, cooled and poured into 100 ml water. The red oil was extracted with ether, washed with dil. NaOH aq and with water and finally concentrated on a steam bath. The viscous red oil in ethanol gave as a first crop material of m.p. 145°. Recrystallization gave 0·2 g (31%) of *phenyldibenzoylmethane* (XVI) of m.p. 149–150°, no depression in melting point with authentic material.

As a second crop 50 mg (7%) red needles, m.p. 151–152°, were collected. This material did not depress the m.p. of an authentic sample of 2, 3-diphenylindenone.

Di- and Tribenzoylmethane with Diphenyliodonium Chloride

Dibenzoylmethane with diphenyliodonium chloride in t-butyl alcohol. After dibenzoylmethane (74 g, 330 mmoles) had been added to a solution of 330 mmoles of potassium t-butoxide in 1200 ml t-butyl alcohol, the mixture was stirred until solution was complete. Diphenyliodonium chloride (104·3 g, 330 mmoles) was added with no appreciable temperature rise, and there was unreacted iodonium salt after 2 hr at room temp. After 5 hr at reflux, the iodonium salt had completely reacted, and t-butyl alcohol (800 ml) was removed by distillation. The residue was diluted with 2 l. water, acidified to pH 6 and repeatedly extracted with ether. Distillation of the dried extract gave three fractions: *A*, 64·2 g crude iodobenzene, b.p. 60–90°/10 mm; *B*, 45·0 g of an oily yellow solid, b.p. 190–220°/0·6 mm; *C*, 22·1 g of a red-brown solid, b.p. 225–235°/0·6 mm.

Crystallization of fraction *B* from ethanol gave 16·2 g unreacted dibenzoylmethane and 15·3 g (51 mmoles, 20%) colorless needles of phenyldibenzoylmethane (XVI) m.p. 147–148°. Recrystallization from methanol–ligroin raised the m.p. to 149–150·5°, reported m.p.'s 119–120°[28] and 149°[21,29]; λ_{max} 246 mμ, ε 34,000.

(Found: C, 84·29; H, 5·37. Calc. for $C_{21}H_{16}O_2$: C, 84·00; H, 5·37%).

Treatment of XVI with aqueous methanolic KOH at 100° for 2 hr gave desoxybenzoin (85%), m.p. 55–56°, and benzoic acid (78%), m.p. 121–122°; neither m.p. was depressed by admixture with an authentic sample.

Treatment of XVI with hydroxylamine hydrochloride in ethanolic pyridine at 100° for 1 hr gave 97% of crude 3, 4, 5-*triphenylisoxazole*, m.p. 201–206°. Recrystallization from acetonitrile raised the m.p. to 209–210°.

(Found: C, 84·77; H, 5·09; N, 4·99. Calc. for $C_{21}H_{15}NO$: C, 84·83; H, 5·08; N, 4·71%).

It has been reported[29] that dehydration of the monoxime of phenyldibenzoylmethane with phosphorus pentachloride gave 3, 4, 5-triphenylisoxazole, m.p. 212°.

Fraction *C* (*vide supra*) was triturated with ligroin and with benzene to give 10·9 g of a light yellow solid, m.p. 128–132°. Recrystallization from methanol gave 8·9 g (29·6 mmoles, 11%) of *phenyldibenzoylmethane* (XVI) m.p. 149–150·5°; the total yield of this compound based on unrecovered dibenzoylmethane was 31%.

The residue (9·4 g) from evaporation of the benzene–ligroin filtrate was distilled to give 7 g of an oil, b.p. 145–150°/0·25 mm, n_D^{25} 1·6169, *o-phenyldibenzoylmethane*, (1, 3-diphenyl-3-phenoxy-2-propene-1-one, XV); λ_{max} 342 and 243 mμ, ε 10,325 and 10,625. The yield of XV based on unrecovered dibenzoylmethane was about 9%. This material on standing slowly decomposes to dibenzoylmethane.

(Found: C, 83·92; H, 5·50. Calc. for $C_{21}H_{16}O_2$: C, 84·00; H, 5·37%).

Treatment of crude XV with aqueous methanolic potassium hydroxide at 100° for 4 hr gave acetophenone (isolated in 23% yield as the 2, 4-dinitrophenylhydrazone, m.p. 248–249°), benzoic acid (63%) m.p. 121–122° and phenol (isolated in 14% yield as 2,4,6-tribromophenol, m.p. 95–96°).

Tribenzoylmethane with diphenyliodonium chloride in t-butyl alcohol. Tribenzoylmethane (65·6 g, 200 mmoles) in 1300 ml t-butyl alcohol in which 7·8 g (200 mg atoms) potassium metal had been dissolved was stirred at room temp. for an hour and gave a deep yellow suspension. Diphenyliodonium chloride (63·2 g 200 mmoles) was added with no appreciable temperature rise. After 48 hr at reflux, the mixture had no unreacted iodonium salt. t-Butyl alcohol (500 ml) was removed by distillation. The mixture was then treated with a solution of 28 g potassium carbonate in 800 ml water and extracted thoroughly with ethyl acetate. The extract was washed with water, dried and concentrated on a steam bath to give a dark brown oil. This oil was boiled with 800 ml ligroin, giving 57·6 g crude product of m.p. 117–121°. This was crystallized from ethanol to give 49·2 g

[28] F. R. Japp and G. D. Lander, *J. Chem. Soc.* **69**, 742 (1896).
[29] J. Marshall, *J. Chem. Soc.* **107**, 521 (1915).

(121 mmoles, 68%) of O-*phenyltribenzoylmethane* (1, 1-dibenzoyl-2-phenoxy-2-phenylethene, XVIII), m.p. 129–130°; infrared spectrum (KBr) showed bands at 6·04 μ (conjugated ketone) and 8·30 μ (C—O-phenolic stretching); λ_{max} 258 mμ, ϵ 27,500.

(Found: C, 83·14; H, 5·10. Calc. for $C_{28}H_{20}O_2$: C, 83·15; H, 4·98%).

Treatment of XVIII with aqueous methanolic potassium hydroxide at reflux for 6 hr gave tribenzoylmethane (9%) m.p. 236–237°, acetophenone (isolated in 14% yield as the 2, 4-dinitrophenylhydrazone, m.p. 248–249°), benzoic acid (70%) m.p. 121–122°, and phenol (isolated in 58% yield as 2, 4, 6-tribromophenol, m.p. 94–95°).

The ligroin filtrate after the removal of XVII (*vide supra*) was then concentrated to about 200 ml and cooled in an acetone dry-ice bath to give an insoluble brown oil which was isolated by decantation. This oil was dried (*in vacuo* for 24 hr over H_2SO_4) to a hard viscous wax, which was dissolved in methanol and gave 7·1 g (17 mmoles), 10% of C-*phenyltribenzoylmethane* (α,α,α-tribenzoyltoluene, XIX), white crystals m.p. 185–187°. Two additional crystallizations from ethanol raised the m.p. to 190–192°, λ_{max} 256 and 321 mμ, ϵ 36,000 and 3005 respectively.

(Found: C, 82·90; H, 5·10. Calc. for $C_{28}H_{20}O_2$: C, 83·15; H, 4·98%).

Treatment of XIX with aqueous methanolic potassium hydroxide at reflux for 5 hr gave 87% of desoxybenzoin m.p. 52–53° (m.p. 55·6° after recrystallization) and 74% of benzoic acid, m.p. 120–121°.

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NEW COMPONENTS OF *CITRUS AURANTIUM*

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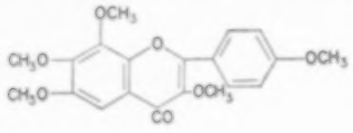
Abstract—Further investigations of the peel of *Citrus aurantium* (from Waltair) have yielded a new flavonoid 5-hydroxyauranetin. 5-O-desmethylnobiletin has been isolated from the peel of Nagpur oranges along with auranetin and hesperidin. These results are of biogenetic significance.

PREVIOUS investigations[1,2] of the peel of Kamala oranges have revealed the presence of auranetin, 3,6,7,8,4′-pentamethoxyflavone (I). Re-investigation has revealed the presence of a new flavonoid shown to be 5-hydroxyauranetin (III). On methylation this gives calycopterin dimethyl ether (5-methoxyauranetin II), which on fission with alkali gives anisic acid and 2-hydroxy-ω-3,4,5,6-penta methoxy acetophenone. The m.p. of III agrees with that of 4′-0-methylcalycopterin (III),[3,4] and the identification was further confirmed by comparison with authentic samples prepared from calycopterin (IV) isolated from the leaves of *Calycopterus floribunda*.[5,6]



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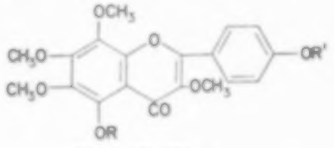
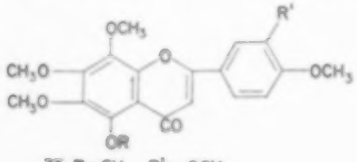
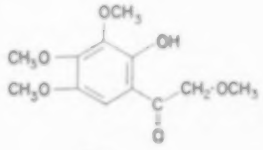


II, R = R′ = CH_3
III, R = H, R′ = CH_3
IV, R = R′ = H

The peel of Nagpur oranges yields auranetin and desmethylnobiletin (VI) which contains one hydroxyl group and five methoxy groups and is isomeric with 5-hydroxy-auranetin. On methylation VI gives nobiletin (V), and on demethylation it gives nornobiletin.[7,8] Partial methylation of the latter gives desmethylnobiletin.[7]



V, R = CH_3, R′ = OCH_3
VI, R = H, R′ = OCH_3
X, R = CH_3, R′ = H



VII

The occurrence of I and III in the peel of *Citrus aurantium* (Waltair variety) is significant. The suggestion was made[2] that the biogenisis of I should closely follow

[1] K. C. Patnayak, S. Rangaswami and T. R. Seshadri, *Proc. Indian Acad. Sci.* **16A**, 10 (1942).
[2] V. V. S. Murti, S. Rangaswami and T. R. Seshadri, *Proc. Indian Acad. Sci.* **28A**, 19 (1948).
[3] R. C. Shah, V. V. Virkar and K. Venkataraman, *J. Indian Chem. Soc.* 135 (1942).
[4] T. R. Seshadri and N. Viswanadham, *Proc. Indian Acad. Sci.* **25A**, 337 (1947).
[5] A. N. Ratnagiriswaran, K. B. Sehra and K. Venkataraman, *Biochem. J.* **28**, 1964 (1934).
[6] T. R. Seshadri and V. Venkateswarlu, *Proc. Indian Acad. Sci.* **23A**, 192 (1946).
[7] R. Robinson and K. F. Tseng, *J. Chem. Soc.* 1004 (1938).
[8] V. V. S. Murti and T. R. Seshadri, *Proc. Indian Acad. Sci.* **27A**, 217 (1948); **30A**, 12 (1949).

that of the related flavonols having substituents in the 5,6,7,8,-positions and belonging to the calycopterin series. The removal of the 5-hydroxyl group in the flavone system has been shown[9] and the nuclear reduction of III has now been achieved by preparing the tosyl derivative which is readily reduced with Raney Nickel to yield auranetin.

The occurrence of V in *Citrus nobilis*[10] and VI with auranetin in *Citrus aurantium* is also significant. It supports the above-mentioned biogenetic relationship and indicates that the final methylation of a resistant 5-hydroxyl group can take place in the plant.

The ketone from alkali fission of auranetin has the constitution VII which has now been established by oxidation[11] to 2-hydroxy-3,4,5-trimethoxybenzoic acid.[12]

Tangeretin, a fully methylated flavone occurring in *Citrus nobilis deliciosa*[13] is a lower member of the nobiletin series (X), and ponkanetin[14] isolated from *Citrus poonensis* Hort is identical with it.[15,16]

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EXPERIMENTAL

Peel of the Waltair variety of Citrus aurantium

Extraction. The air dried peel (2 kg) was extracted twice with light petroleum (b.p. 60–80°) for 24 hr in the cold to remove essential oils and fatty and waxy material. The extraction was repeated thrice with more light petroleum by refluxing for 10 hr each time. The hot extract after concentration deposited a pale yellow solid which was filtered, taken up in ether and the ether solution extracted with 5% NaOH (fraction A). Evaporation of the remaining ether solution yielded a neutral fraction B.

The residual peel was extracted with boiling alcohol for 10 hr. The alcoholic extract was evaporated under reduced pressure to a reddish brown concentrate. This was extracted with ether leaving an insoluble residue (fraction C). The etheral solution extracted with 5% NaOH aq. again yielded fraction A, and the residual ether solution yielded fraction B.

Fraction A (*5-hydroxy auranetin*, III). Acidification yielded a yellow solid, which crystallized from alcohol as yellow prisms, m.p. 125–27°. In alcoholic solution it gave a red colour with magnesium or zinc and hydrochloric acid and an olive green colour with ferric chloride (Found: C, 61·9; H, 5·3, OCH_3, 39·0, Calc. for $C_{20}H_{20}O_8$: C, 61·9; H, 5·2; OCH_3, 40%). Yield, 0·25 g. Mixed m.p. with an authentic sample of 5-hydroxy auranetin (4′-O-methyl calycopterin[4]) was undepressed.

Methylation of A *to* (*5-methoxy auranetin* II). The above compound (0·1 g) was refluxed with acetone (100 cc), dimethyl sulphate (2 cc), and potassium carbonate (5 g) for 40 hr. The methyl ether crystallized from ethyl acetate–light petroleum mixture as colourless plates, m.p. 132–34° (Found: C, 62·4; H, 5·6; Calc. for $C_{21}H_{22}O_8$: C, 62·7; H, 5·5%). Mixed m.p. with a synthetic sample of calycopterin dimethyl ether was undepressed. The infra-red spectrum showed peaks at (microns) 6·1 (S), 6·2 (S), 6·3 (W), 6·7, 7·1 (S), 7·9 (S) 8·5 (S), 8·8 (W), 9·3, 9·5 (S), 11·9 (S), 12·7 (W).

Fission of methyl ether (II) *to 2-hydroxy-ω-3:4:5:6-pentamethoxy-acetophenone.* The methyl ether (0·05 g) was boiled under reflux with 8% absolute alcoholic potash for 6 hr. The sodium bicarbonate soluble fraction yielded anisic acid, m.p. and mixed m.p. 182–84°. The ketonic product gave a green colour with ferric chloride. It was isolated as the 2:4-dinitro-phenylhydrazone, m.p. 173–75°.[6]

Tosylation of A. The hydroxy compound (0·13 g) in acetone (100 cc) was refluxed with *p*-toluene sulphonyl chloride (0·3 g) and potassium carbonate (10 g) on a water bath until the product gave no colour with alcoholic ferric chloride (16 hr). The tosyl ester crystallized from alcohol as colourless prisms, m.p. 165–67° (Found: C, 60·2; H, 4·6; $C_{27}H_{26}SO_{10}$ requires: C, 59·8; H, 4·8%).

Raney nickel reduction. The tosyl ester (0·07 g) was dissolved in alcohol (300 cc) and Raney

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[17] V. V. S. Murti, K. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.* **24A**, 233 (1946).

nickel[18] (two teaspoonfuls) added. A stream of purified hydrogen was passed for 1 hr with vigorous shaking. The alkali insoluble product crystallized from alcohol as colourless needles, m.p. 139–40°. Mixed m.p. with an authentic sample of auranetin was undepressed. Comparison of the infra-red spectra of the nuclear reduction product and auranetin confirmed identity.

Fraction B (*auranetin* I). Complete evaporation of the ether solution left a pale yellow solid which crystallized from alcohol as colourless needles, m.p. 139–40°. It gave no colour with alcoholic ferric chloride. Yield 1·0 g (Found: C, 64·8; H, 5·7; Calc. for $C_{20}H_{20}O_7$: C, 64·5; H, 5·4%). The infra-red spectrum showed the following peaks at (microns) 6·1 (S), 6·7 (W), 7·3 (S), 7·7 (W), 7·8 (S), 9·3 (S), 9·8 (S), 10·3 (W), 11·9, 12·3 (W).

Demethylation of fraction B using hydriodic acid yielded a product which was identical with norauranetin in all respects.

Fission of auranetin to 2-hydroxy-ω:3:4:5-tetramethoxy-acetophenone (VII). (0·75 g) in absolute alcoholic potash (2 g in 25 cc) was refluxed on a water bath. The bicarbonate soluble fraction gave anisic acid, m.p. and mixed m.p. 182–84°. The potash soluble fraction (hydroxy-ketone) crystallized from alcohol as pale yellow prisms, m.p. 116–17°. It gave a brown colour with alcoholic ferric chloride (Found: C, 56·5; H, 6·5, OCH_3, 48·6; $C_{12}H_{16}O_6$ requires: C, 56·2; H, 6·3, OCH_3, 48·5%).

Oxidation of the ketone to 2-hydroxy-3:4:5-trimethoxy benzoic acid (VIII). A mixture of the above ketone (0·2 g), iodine (0·8 g) and pyridine (5 cc) was heated in a steam bath for 1 hr and then kept at 0° for 24 hr. The alcoholic solution of the pyridinium iodide complex was heated with aqueous potash (2%, 25 cc) in a steam bath for 1 hr. The acid product crystallized from ethyl acetate–light petroleum mixture as colourless needles, m.p. 190–92° (decomp). Mixed m.p. with an authentic sample of 2-hydroxy-3:4:5-trimethoxy benzoic acid[18] was undepressed.

The above method of oxidation had not been used with ω-methoxy acetophenones. Hence ω-methoxy phloroacetophenone dimethyl ether was used for test experiment under identical conditions and it gave 4:6-dimethoxy salicylic acid, m.p. 152–54° (decomp); Josephson[19] also reported the same m.p. for the sample obtained by a different method.

Fraction C (*hesperidin*). This was sparingly soluble in most solvents and was crystallized from pyridine; the colourless crystalline solid melted at 250–51° (2·5 g). Its reactions agreed with those of hesperidin and the mixed m.p. with an authentic sample was undepressed.

Peel of Nagpur variety

The extraction of the air dried peel was repeated. The petroleum ether extract gave a 5% NaOH soluble fraction A′ and a neutral fraction B′. The alcoholic extract gave in addition to the above two components, a glycosidic fraction C′.

Fraction A′ (5-O-*desmethyl nobiletin* VI). This fraction crystallized from alcohol as colourless needles, m.p. 144–46° (0·5 g). It gave a deep red colour with magnesium and alcoholic hydrochloric acid and a green colour with alcoholic ferric chloride (Found: C, 61·5; H, 5·6; OCH_3, 40·8; Calc. for $C_{20}H_{20}O_8$: C, 61·9; H, 5·2; OCH_3, 40%). Robinson and Tseng[7] reported the same m.p.

Methyl ether of A′ (*nobiletin* V). The methylation of the above compound was effected with dimethyl sulphate using acetone and potassium carbonate by refluxing for 54 hr. The product crystallized from ethyl acetate as pale yellow prisms, m.p. 129–31°. It gave no colour with alcoholic ferric chloride. (Found: C, 62·5; H, 5·7; Calc. for $C_{21}H_{22}O_8$: C, 62·7; H, 5·5%).

The fission of the methyl ether (0·1 g) was effected by refluxing with alcoholic potash (20 cc, 20%) for 4 hr. The sodium bicarbonate soluble fraction gave veratric acid, m.p. and mixed m.p. 179–80°.

Demethylation of A′ *to nornobiletin*. Compound A′ (0·2 g) was boiled with hydriodic acid (8 cc) and acetic anhydride (20 cc). The hydroxy flavone so obtained crystallized from absolute alcohol as yellow prisms, m.p. 310–12° (decomp). It gave an olive green colour with alcoholic ferric chloride and agreed in chromatographic behaviour (circular R_f 0·37, with butanol, acetic acid and water at 28°) as well as other colour reactions with a synthetic sample of nornobiletin.[8]

The norcompound, on acetylation with acetic anhydride in pyridine, gave the acetate which crystallized from alcohol as colourless needles, m.p. 226–28°.[7]

Fraction B′ (*auranetin*, I). This fraction crystallized from alcohol as colourless needles, m.p. 139–140° (0·5 g). Mixed m.p. with auranetin was undepressed.

Fraction C′ (*hesperidin*). It crystallized from pyridine, m.p. 250–51° and agreed with an authentic sample of hesperidin in all respects.

[18] R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, *J. Amer. Chem. Soc.* **65**, 1015 (1943).
[19] K. Josephson, *Arkiv Kemi, Min. Geol.* **36**, 11 (1927).

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THE SYNTHESIS OF 1-, 2- AND 3-TRIFLUOROMETHYL-CARBAZOLES BY THE FISCHER–INDOLE METHOD

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Abstract—1-, 2-, and 3-Trifluoromethylcarbazoles have been obtained from the corresponding tetrahydrocarbazoles, which were made by the Fischer–indole method. Cyclization of cyclohexanone-*m*-trifluoromethylphenylhydrazone gave only one tetrahydrocarbazole: this afforded 2-trifluoromethylcarbazole.

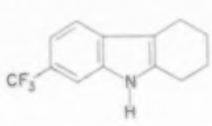
THE biological activity of compounds containing the trifluoromethyl group has hardly been studied. We decided therefore to make a number of trifluoromethylanalogues of heterocyclic compounds of biological importance. Our first efforts, directed towards analogues of tryptophane and serotonin, were unsuccessful. The difficulty of obtaining suitable tri-substituted benzenes, containing the trifluoromethyl group, and the general instability of the trifluoromethyl group towards Lewis acids makes the Fischer–indole route the most reasonable approach to these compounds. However, the deactiviting effect of the trifluoromethyl group on the benzene nucleus either precludes the formation of simple indoles or renders their formation very difficult by this method. The phenylhydrazones of cyclohexanone however usually cyclize more readily than those of other carbonyl compounds, and in this respect the trifluoromethylphenylhydrazones were not exceptional. They afforded fairly good yields of tetrahydrocarbazoles from which were obtained 1-, 2-, and 3-trifluoromethyl carbazoles.

m-Trifluoromethylphenylhydrazine, the most accessible member of the series, was obtained by a modification of the method of Bornstein *et al.*[1] It formed with cyclohexanone a hydrazone which proved to be very unstable in light and air, but which on treatment with acid gave a good yield of only one tetrahydrocarbazole (I), whose ultraviolet spectrum closely resembled that of tetrahydrocarbazole itself. Dehydrogenation of the tetrahydrocarbazole failed using Raney nickel, but proceeded smoothly with chloranil in boiling xylene. The carbazole produced was shown later by an unequivocal synthesis[2] to be the 2-trifluoromethyl isomer; a comparison being made between their N-acetyl derivatives. The acetylation of 2-trifluoromethylcarbazole, as with the other isomers, proceeded smoothly with acetic anhydride, when catalytic amounts of zinc chloride or perchloric acid,[3] but not sulphuric acid were used.

The preparations of *o*-, and *p*-aminotrifluoro methylbenzenes are somewhat tedious. Of the several methods available[4–6] for the preparation of the *para* isomer, perhaps the most convenient is that of Pouterman and Girardet.[5] It involves the

[1] J. Bornstein, S. A. Leone, W. F. Sullivan and A. F. Bennett, *J. Amer. Chem. Soc.* **79**,1745 (1957).
[2] Succeeding Paper: *Tetrahedron* **8**, 73 (1960).
[3] F. Kehrmann and E. Baumgartner, *Helv. Chim. Acta* **9**, 673 (1926); A. A. Berlin, *Chem. Abstr.* **39**, 4606 (1945).
[4] R. G. Jones, *J. Amer. Chem. Soc.* **69**, 2346 (1947).
[5] E. Pouterman and A. Girardet, *Helv. Chim. Acta.* **30**, 107 (1947).
[6] Brit. Pat., 459881 and 459,890.

deamination of 3-amino-4-nitrotrifluoromethylbenzene followed by reduction of the nitro compound. Reduction of the diazonium salt from *p*-aminotrifluoromethylbenzene with ammonium sulphite gave a much better yield (79%) of *p*-trifluoromethylphenylhydrazine than did that using stannous chloride (43%). This is in keeping with the fact that in general the reduction of diazonium ions containing powerful electron withdrawing substituents in the *ortho*- or *para*-positions gives low yields of hydrazine using stannous chloride.[7] The preparation of cyclohexanone-*p*-trifluorophenylhydrazone and its conversion into 6-trifluoromethyltetrahydrocarbazole proceeded



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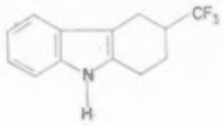

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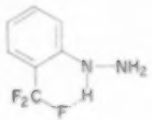

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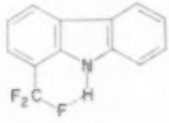

IV

normally. Again dehydrogenation of the tetrahydro compound succeeded with chloranil but not with Raney nickel. 3-Trifluoromethylcarbazole thereby obtained was shown to be identical with a specimen obtained by the dehydrogenation of 3-trifluoromethyl-1,2,3,4-tetrahydrocarbazole (II) obtained from the phenylhydrazone of 4-trifluoromethylcyclohexanone.[8]

o-Trifluoromethylaniline was obtained from *m*-acetamidotrifluoromethylbenzene. Nitration of this compound[9] with fuming nitric acid in sulphuric acid gave 5-amino-2-nitrotrifluoromethylbenzene after subsequent hydrolysis of the product with 50 per cent sulphuric acid. Hydrolysis of the amide with alkali[9] afforded a much inferior yield of amine. Deamination of the amine was best effected by a modification of the method of Hodgson and Turner.[10] The amine was diazotized with ethyl nitrite and the diazonium salt was reduced with copper bronze in ethanol to give a high yield of *o*-nitrotrifluoromethylbenzene. Reduction of this nitro-compound with Raney nickel and the subsequent conversion of *o*-trifluoromethylaniline into *o*-trifluoromethylphenylhydrazine proceeded normally. Again the use of ammonium sulphite at pH 6–7 rather than stannous chloride under acid conditions gave a better yield of hydrazine from the diazonium compound.

o-Trifluoromethylphenylhydrazine reacts more slowly with carbonyl compounds than do the other isomers. Steric effects may well be operative, but the compound is probably a weaker base than the other hydrazines due to possible intramolecular hydrogen bonding (III). Cyclization of its anil with cyclohexanone gave 8-trifluoromethyl-1,2,3,4-tetrahydrocabrazole as a liquid, which could not be induced to crystallize. In this respect it differs from the other members of the series which are fairly high

[7] K. H. Saunders, *The Aromatic Diazo-compounds* (2nd Ed.) pp. 184–185. Edward Arnold, London (1949).
[8] F. L. Turner, Ph.D. Thesis, Birmingham University (1958).
[9] H. Rouche, *Bull. Sci. Acad. Roy. Belg.* [5], **13**, 346 (1927).
[10] H. H. Hodgson and H. S. Turner, *J. Chem. Soc.* 10 (1944).

melting solids. Moreover it was appreciably less stable towards heat than the other tetrahydro-compounds, and its dehydrogenation to 1-trifluoromethylcarbazole proved difficult. The usual agents—Raney nickel, palladized charcoal or chloranil—gave either starting material or decomposition products. Success was finally achieved using sulphur in boiling quinoline, a method previously used in this series by Plant and Oakeshott.[11] Again, 1-trifluoromethylcarbazole (IV) is a much lower melting solid than the other members of this series, and surprisingly it deteriorates on keeping. These results and those for the tetrahydro-compound may well be due to hydrogen bonding, illustrated for the carbazole itself (IV). Apart from its elemental analysis, its ultra-violet spectrum and its colour reactions leave no doubt that it is a carbazole. The ultra-violet spectra of the tetrahydrocarbazoles closely resemble that of the parent compound but display a small bathochromic shift. The ultra-violet spectra of the carbazoles all resemble that of carbazole itself with a characteristic series of bands.

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EXPERIMENTAL

Ultra-violet spectra were measured in ethanol.

m-*Trifluorophenylhydrazine*

The hydrogenation of *m*-nitrotrifluoromethylbenzene in methanol using Raney nickel catalyst at 100°/100 atm afforded *m*-aminotrifluoromethylbenzene (92%), b.p. 79–82°/15 mm. A solution of sodium nitrite (82 g) in water (160 cc) was added to a vigorously stirred suspension of amine hydrochloride [from amine (147 g)] in a mixture of conc HCl (400 cc) and water (270 cc) at 5°. After 15 min the diazo-solution was poured slowly with stirring into a solution of stannous chloride dihydrate (530 g) in conc HCl (530 cc). After being stirred for a further 10 min, the solution was diluted with water, filtered and then rendered alkaline with 4 N NaOH. After working up the mixture in the usual manner *m*-trifluorophenylhydrazine was obtained as a pale-yellow liquid (110 g, 69%), b.p. 138–140°/14 mm Bornstein *et al.*[1] cite b.p. 80–83°/9 mm.

The *hydrochloride* was obtained by treating an ethereal solution of the base with dry hydrogen chloride. It crystallized in leaflets from ethyl acetate–light petroleum, m.p. 224–225° (decomp) (Found: C, 39·5; H, 3·9; F, 27·2. $C_7H_8N_2F_3Cl$ requires: C, 39.5; H, 3·8; F, 26·9%).

The *benzoyl* derivative, made by the Schotten–Baumann method crystallized from ethanol in long needles, m.p. 178–179° (Found: C, 59·6; H, 3·8. $C_{14}H_{11}N_2OF_3$ requires: C, 60·0; H, 3·9%).

The *benzylidene* derivative, prepared in methanol, crystallized from methanol as a yellow microcrystalline solid, m.p. 89–90° (Found: C, 63·7; H, 4·1. $C_{14}H_{11}N_2F_3$ requires: C, 63·7; H, 4·2%).

7-*Trifluoromethyl*-1,2,3,4-*tetrahydrocarbazole*

When *m*-trifluoromethylphenylhydrazine hydrochloride (1·0 g) in methanol (2 cc, containing a drop of HCl) was treated with cyclohexanone (0·5 g) a vigorous exothermic reaction ensued. The yellow precipitate so formed was recrystallized several times from methanol (charcoal) to afford colourless needles of the *m*-trifluorophenylhydrazone (0·6 g), m.p. 139°. It was unstable in light and air and could not be analysed.

A mixture of the hydrazone (0·5 g), conc H_2SO_4 (1·0 cc) and glacial acetic acid (6·0 cc) was maintained at 75–85° for 30 min. On pouring the cooled solution into water, a precipitate was formed. This was filtered off, washed with water, and recrystallized from ethanol to give colourless plates of 7-trifluoromethyl-1,2,3,4-tetrahydrocarbazole (0·3 g), m.p. 124–127°. It decomposed rapidly in light and air and could not be analysed.

Light absorption: λ_{max} 292 mμ, log ϵ_{max} 3·69.

2-*Trifluoromethylcarbazole*.

A solution of 7-trifluoromethyl-1,2,3,4-tetrahydrocarbazole (0·75 g) and chloranil (1·5 g, 2 moles) in a minimum of sulphur-free xylene was boiled under reflux until the liquid no longer gave a red colour with warm 2 N NaOH (ca. 4 hr).

[11] S. H. Oakeshott and S. G. P. Plant, *J. Chem. Soc.* 1210 (1926).

The cooled solution was filtered and, after being diluted with ether, was washed several times with 2 N NaOH and finally with water. It was dried and evaporated to leave a semi-solid residue which sublimed at 120°/0·1 mm. Recrystallization of the sublimate from benzene afforded colourless leaflets of *2-trifluoromethylcarbazole*, (0·3 g), m.p. 209–210° (Found: C, 66·7; H, 3·4; F, 23·8. $C_{13}H_8NF_3$ requires: C, 66·4; H, 3·5; F, 24·2%). Light absorption: λ_{max} 234, 236, 238, 249, 258 and 295 mμ.

The N-acetyl derivative was made by heating a mixture of the carbazole (0·1 g) and a catalytic amount of anhydrous zinc chloride in acetic anhydride (3 cc) for 20 min. The cooled solution was poured into water (20 cc) and the mixture was worked up in the usual manner to afford the N-acetyl derivative as small colourless needles from light petroleum (b.p. 60–80°), m.p. 122–123°, undepressed on admixture with an authentic specimen[8] (Found: C, 65·0; H, 3·5. $C_{15}H_{10}ONF_3$ requires: C, 65·0; H, 3·6%). Light absorption: λ_{max} 267, 287, 306 and 318 mμ; log ε 4·2, 4·16, 3·76 and 3·8 respectively.

p-*Aminotrifluoromethylbenzene*

(a) A solution of *p*-nitrotrifluoromethylbenzene (51·0 g) in light petroleum (b.p. 40–60°) was hydrogenated at 100°/100 atm using Raney nickel catalyst. When reduction was complete (ca. 4 hr) the mixture was worked up in the usual manner to afford the amine (30 g), b.p. 85–88°/16 mm.

(b) An intimate mixture of N-(*p*-trichloromethylphenyl) phthalimide (92 g)[6] and antimony trifluoride (48 g) was melted and gently heated under reflux for a further 10 min. The cooled mixture was extracted with boiling ethanol (250 cc) and the extract was poured into dil HCl. The resultant precipitate was treated with 6 N HCl, and the mixture was filtered. A solution of the residue in boiling ethanol was poured into cold water. After standing for 2 hr at 0°, the trifluoro–imide was obtained as a pale-yellow solid, m.p. 128–131° (30 g, 38%). The trifluoro-imide (100 g) was heated in a current of steam with 12% hydrazine hydrate (230 cc) for 12 hr. Working up the distillate in the usual manner gave *p*-aminotrifluoromethylbenzene (15 g, 27%), b.p. 86–88°/15 mm. When the trichloro-compound was treated with liquid hydrogen fluoride,[6] the trifluoro-imide was obtained in only 15% yield.

p-*Trifluoromethylphenylhydrazine*

(a) *p*-Aminotrifluoromethylbenzene was diazotized and the diazo-compound reduced with stannous chloride as for the *meta*-isomer. A solution of the hydrazine, so obtained, in ether was treated with anhydrous hydrogen chloride to give p-*trifluoromethylphenylhydrazine hydrochloride* as a colourless solid which crystallized from ethanol–ether in leaflets (1·2 g, 43%), m.p. 206–207° (decomp) (Found: C, 39·2; H, 3·3; F, 27·0. $C_7H_8N_2F_3Cl$ requires: C, 39·5; H, 3·7; F, 26·9%).

(b) A fine suspension of amine hydrochloride [from amine (11·0 g)] in conc HCl (20 cc) was treated with a solution of sodium nitrite (6·0 g) in water (24 cc) at 0–5°. After 15 min the diazo-solution was brought to pH 6·5 with N Na_2CO_3 and poured rapidly into a solution of ammonium sulphite (60 cc, made by saturating aqueous ammonia, *d* 0·880, with sulphur dioxide at 0°) keeping the temperature below 5°. The solution was stirred for 1 hr at room temp and was then heated on a steam-bath with conc HCl (25 cc) until no more sulphur dioxide was evolved. After boiling it under reflux the solution was cooled and rendered alkaline with 4 N NaOH (cooling). The mixture was extracted with ether and worked up in the usual manner to afford *p*-trifluoromethylphenylhydrazine (9·5 g, 79%) as long colourless needles from light-petroleum (b.p. 40–60°), m.p. 59–60°, whose hydrochloride was identical with that prepared by method (a).

The *benzylidene* derivative, prepared in methanol, crystallized from methanol in colourless needles, m.p. 129–130° (Found: C, 63·3; H, 4·2. $C_{14}H_{11}N_2F_3$ requires: C, 63·7; H, 4·2%).

6-*Trifluoromethyl*-1,2,3,4-*tetrahydrocarbazole*

A mixture of *p*-trifluoromethylphenylhydrazine (1·0 g), cyclohexanone (1·0 g) and ethanol (4 cc) containing conc HCl (2 drops) was heated on a water bath for 1 min. The precipitate was collected, washed with water and recrystallized from methanol to give small yellow needles of cyclohexanone-*p*-trifluoromethylphenylhydrazone, m.p. 155–158° (too unstable for analysis).

A solution of the hydrazone (1·0 g) in conc H_2SO_4 (1·0 cc) and glacial acetic acid (6·0 cc) was heated on a steam bath for 30 min. The cooled solution was diluted with water (100 cc) and filtered. The solid was collected, washed with water and dried. It distilled at 140–142°/0·1 mm to give a pale-yellow distillate which solidified in the receiver. The distillate crystallized from light-petroleum (b.p. 60–80°) to afford 6-*trifluoromethyl*-1,2,3,4-*tetrahydrocarbazole* as colourless glistening needles (0·5 g, 40%),

m.p. 83–84° (Found: C, 65·4; H, 5·0. $C_{13}H_{12}NF_3$ requires: C, 65·3; H, 5·0%). Light absorption: λ_{max} 283 mμ, log ε 4.37.

3-Trifluoromethylcarbazole

A solution of chloranil (0·8 g) and the tetrahydro-compound (0·4 g) in purified xylene was boiled under reflux until it no longer gave a colour with warm 2 N NaOH (ca. 6 hr). The cooled solution was filtered and diluted with ether. After being shaken several times with 2 N NaOH, the organic phase was dried and evaporated. On heating at 115°/0·1 mm, the residue sublimed to give *3-trifluoromethylcarbazole* as a solid, which crystallized from light petroleum (b.p. 80–100°) in colourless needles, m.p. 166–167° (Found: C, 66·2; H, 3·7. $C_{13}H_8NF_3$ requires: C, 66·4; H, 3·4%). The compound showed no m.p. depression on admixture with a specimen obtained from the phenylhydrazone of 4-trifluoromethylcyclohexanone.[8] Light absorption: λ_{max} 236, 262, 295, 312 and 320 mμ; log ε 3·87, 3·81, 3·31, 2·67 and 2·81.

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5-Amino-2-nitrotrifluoromethylbenzene

A mixture of fuming nitric acid (76 cc) and conc H_2SO_4 (130 cc) was added with stirring to a solution of *m*-acetylaminotrifluoromethylbenzene (255 g) in conc H_2SO_4 (1360 cc) over a period of 45 min, the temp being kept below 5°. After standing for 15 hr at room temp, the mixture was warmed at 40° for 1 hr, and was then poured on to crushed ice (ca. 4 kg). 5-Acetylamino-2-nitrotrifluoromethylbenzene was thereby obtained as a yellow solid (270 g).

A mixture of the acetyl compound (100 g), conc H_2SO_4 (283 cc) and water (480 cc) was heated on a steam-bath for 2 hr, and then boiled for 1 hr. On pouring the cooled solution into water at 0°, 5-amino-2-nitrotrifluoromethylbenzene was obtained as a solid, which crystallized from aqueous-ethanol in yellow needles (60 g, 70%), m.p. 124–126°.

2-Nitrotrifluoromethylbenzene

5-Amino-2-nitrotrifluoromethylbenzene (57·8 g) was added with stirring to a solution of conc H_2SO_4 (31 cc) in ethanol (225 cc) at 0°. Ethyl nitrite (42 g) was added with cooling over 1 hr to the suspension of amine sulphate thus formed. After standing for 1 hr at 5°, the solution was allowed to come to room temp and was then treated with copper bronze (0·45 g). Evolution of nitrogen then ensued smoothly for ca. 2 hr, while the temp of the solution was kept below 40°. After being boiled for 15 min, the solution was cooled and diluted with water. The organic phase was separated and added to the combined chloroform extracts (4 × 100 cc) of the aqueous layer. Removal of the solvents and distillation of the residue afforded 2-nitrotrifluoromethylbenzene (43·7 g, 82%), b.p. 100–102°/15 mm, m.p. 28–30°.

When 5-amino-2-nitrotrifluoromethylbenzene was deaminated according to the method of Hodgson and Turner[10] the yield of 2-nitrotrifluoromethylbenzene was 40%.

o-Aminotrifluoromethylbenzene

A solution of 2-nitrotrifluoromethylbenzene (160 g) in light petroleum (b.p. 60–80°) was hydrogenated at 120°/100 atm using Raney nickel catalyst (ca. 10 g). The filtered solution was distilled to yield *o*-aminotrifluoromethylbenzene (111 g, 82%) as a colourless liquid, b.p. 77–80°/15 mm.

o-Trifluoromethylphenylhydrazine

A stirred suspension of *o*-aminotrifluoromethylbenzene hydrochloride [from amine (5·5 g)] in conc HCl (10 cc) and water (5 cc) was treated with a solution of sodium nitrite (3·0 g) in water (6·0 cc) at 0°. After being kept for 15 min, the diazo-solution was added slowly to a solution of ammonium sulphite (30 cc) at 0–5°. When the mixture had stood for 20 min, it was treated with conc HCl (20 cc) and boiled until the evolution of sulphur dioxide had ceased. The cooled solution was diluted with water, filtered from tar, and rendered alkaline with 4 N NaOH. The mixture was extracted with ether, and the ethanol extract was dried and treated with dry hydrogen chloride. *o-Trifluoromethylphenylhydrazine hydrochloride* was thereby obtained as a solid (5·3 g, 74%) which crystallized from water or methanol in colourless plates, m.p. 218° (decomp) (Found: C, 39·3; H, 3·9. $C_7H_8N_2F_3Cl$ requires: C, 39·5; H, 3·8%).

The *base* crystallized from light petroleum (b.p. 40–60°) in long colourless needles, m.p. 61–62° (Found: C, 48·2; H, 4·1; F, 32·1. $C_7H_7N_2F_3$ requires: C, 47·7; H, 4·0; F, 32·4%).

When the reduction of the diazonium salt was effected with stannous chloride the yield of *o*-trifluoromethylphenylhydrazine was 30%.

8-Trifluoromethyl-1,2,3,4-tetrahydrocarbazole

A mixture of cyclohexanone (3 cc), *o*-trifluoromethylphenylhydrazine hydrochloride (3·5 g) and glacial acetic acid (10 cc) was maintained at 100° for 10 min. Dry hydrogen chloride was then passed through the mixture for 10 min, when it was cooled and poured into water (50 cc). The mixture was extracted with ether (2 × 50 cc), and the combined ethereal extracts were washed with 2 N Na_2CO_3 and dried. After removal of the solvents, the residue was fractionated to give *8-trifluoromethyl-1,2,3,4-tetrahydrocarbazole* as a pale-yellow oil (3·0 g, 77%), b.p. 148–150°/2 mm. (Found: C, 65·0; H, 5·3; F, 23·3. $C_{13}H_{12}NF_3$ requires: C, 65·3; H, 5·0; F, 23·8%).

1-Trifluoromethylcarbazole

A suspension of sulphur (0·4 g) in a solution of the tetrahydrocarbazole (1·0 g) in quinoline (10 cc) was heated under reflux until no more hydrogen sulphide was evolved (ca. 45 min). The cooled mixture was poured on to a mixture of ice (50 g) and 2 N HCl (20 cc), and the whole was extracted several times with ether. The combined ethereal extracts were dried and distilled to give *1-trifluoromethylcarbazole* (0·15 g) as a pale-yellow liquid b.p. 85–88°/0·1 mm, which set to a waxy solid, m.p. 49–50° (Found: C, 66·2; H, 3·7. $C_{13}H_8NF_3$ requires: C, 66·3; H, 3·5%). Light absorption λ_{max} 235, 262 and 295 mμ; log ε 3·49, 3·21, 3·14 respectively.

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THE UNEQUIVOCAL SYNTHESES OF 2- AND 4-TRIFLUOROMETHYLCARBAZOLES VIA DIPHENYLS

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(*Received* 28 *July* 1959)

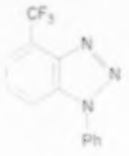
Abstract—4- and 6-Trifluoromethyl-1-phenylbenzotriazoles have been prepared by standard methods. They do not decompose to give carbazoles. 2-Nitro-4-trifluoromethyldiphenyl and 2′-nitro-2-trifluoromethyldiphenyl have been reduced to the amines which were diazotized and converted into azides. The former decomposes in ultra-violet light to give 2-trifluoromethylcarbazole, the latter decomposes on heating to give 4-trifluoromethylcarbazole.

WHEN the *m*-trifluoromethylphenylhydrazone of cyclohexanone was treated with a mixture of sulphuric acid and acetic acid, it yielded only one tetrahydro-carbazole, which was converted into the carbazole.[1] According to whether the cyclization of the hydrazone occurred *ortho* or *para* to the trifluoromethyl group this carbazole would be the 4- or 2-trifluoromethylcarbazole. Unequivocal syntheses of these two compounds has now shown that the original carbazole is in fact the 2-trifluoromethyl isomer. This means that the cyclization of the hydrazone occurs mainly *para* to the trifluoromethyl group (yield of tetrahydrocarbazole 70 per cent), which recalls the preferential formation of 7-trifluoromethylquinoline from *m*-trifluoromethylaniline in the Skraup reaction[2] (ratio of 7- to 5-trifluoromethyl isomers is 5 : 1). These results are probably determined by electronic rather than steric influences, for it is certain that the deactivating effect of the dipole associated with the trifluoromethyl group will be more strongly felt in the *ortho* position than in the *para* position. The formation of 4-trifluoromethylisatin (30 per cent: the other isomer was not detected) from *m*-trifluoromethylisonitroso acetanilide[3] remains anomolous.

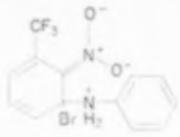
We first attempted to prepare these carbazoles by the thermal decomposition of the requisite benzotriazoles. 1-Phenyl-4-trifluoromethylbenzotriazole (I) was made as follows. 3-Bromo-2-nitrotrifluoromethylbenzene was heated with an excess of aniline in the presence of cuprous bromide and potassium carbonate. 2-Nitro-3-trifluoromethyldiphenylamine was thereby obtained in no more than 19 per cent yield. This diphenylamine was better prepared by heating 3-amino-2-nitrotrifluoromethylbenzene with excess aniline under the same conditions as above when the yield was raised to 52 per cent. This difference in yield may be accounted for by considerations of the transition states of the two reactions. The former would receive a major contribution from the form (II) in which the NO_2 entity is planar to the benzene ring. Steric interaction with the trifluoromethyl group will however prevent its formation

[1] Preceding paper: *Tetrahedron* **8**, 67 (1960).
[2] H. Gilman and D. T. Blume, *J. Amer. Chem. Soc.* **65**, 2467 (1943); R. Belcher, M. Stacey, A. Sykes and J. C. Tatlow, *J. Chem. Soc.* 3846 (1954).
[3] B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy and J. H. Williams, *J. Org. Chem.* **17**, 164 (1952).

and so destabilize the transition state. Such considerations do not apply to the second reaction.



I

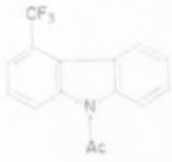


II

2-Nitro-3-trifluoromethyldiphenylamine was reduced catalytically to the amine, which was diazotized in the usual manner to afford the triazole (I), which when treated in a variety of ways, including heating to 300° with *m*-dinitrobenzene,[4] yielded no carbazole. The conditions either gave starting material or resulted in extensive decomposition. 2-Nitro-5-trifluoromethyldiphenylamine was prepared in good yield from 3-amino-4-nitrotrifluoromethylbenzene and bromobenzene. Its conversion into 1-phenyl-6-trifluoromethylbenzotriazole was analogous to the preparation of the 4-trifluoromethyl isomer from 3-trifluoromethyl-2-nitrodiphenyl. Under a variety of conditions, 1-phenyl-6-trifluoromethylbenzotriazole also failed to form a carbazole. The difficulty of obtaining carbazoles by this method when the triazole contains electro-withdrawing substituents has been noticed previously.[5]

A number of carbazoles have been prepared in good yield by decomposing *o*-azidodiphenyls (III) with heat or ultra-violet light.[6] When this method was applied to the preparation of the trifluoromethyl carbazoles it was successful. 2-Nitro-4-trifluoromethyldiphenyl was obtained by diazotizing 4-amino-3-nitrotrifluoromethylbenzene[7] and coupling the diazo-compound with benzene in the presence of sodium acetate. The nitrodiphenyl was reduced catalytically and the resulting 2-amino-4-trifluoromethyldiphenyl diazotized in the usual manner. When the diazo-solution was treated with sodium azide, 2-azido-4-trifluoromethyldiphenyl was obtained as an oil. Its dilute solution in tetralin was irradiated in a quartz vessel with ultra-violet light. After a brief induction period nitrogen was evolved steadily. 2-Trifluoromethylcarbazole was thereby produced in 45 per cent yield, and proved to be identical with the carbazole obtained by dehydrogenating the tetrahydrocarbazole obtained from the *m*-trifluoromethylphenylhydrazone of cyclohexanone.[1]

III



IV

4-Trifluoromethylcarbazole was made analogously. The diphenyl required for the preparation of this carbazole was obtained from *o*-iodotrifluoromethylbenzene (of which a sample was available) and *o*-nitrobromobenzene by the Ullmann procedure.

[4] B. Starkova, A. Vystrcil and L. Starka, *Chem. Listy* 536 (1957).
[5] R. C. Elderfield, *Heterocyclic Compounds* p. 298. John Wiley, New York (1952).
[6] P. A. S. Smith and B. B. Brown, *J. Amer. Chem. Soc.* **73**, 2435 (1951).
[7] M. R. Pettit and J. C. Tatlow, *J. Chem. Soc.* 3852 (1954).

Fractional crystallization of the reaction mixture served to separate 2,-2′-dinitrodiphenyl, and chromatography on alumina of the residue afforded 2-nitro-2′-trifluoromethyldiphenyl (14 per cent). This was converted into 2-azido-2′-trifluoromethyldiphenyl in the manner described for the other isomer. Again the azide was obtained as an oil, which was not purified. When a dilute solution of this azide in tetralin was irradiated with ultra-violet light nitrogen was evolved, but no carbazole could be isolated from the reaction mixture; indeed colour reactions failed to detect any carbazole in the product. When the decomposition of the azide was carried out thermally in decalin at 180–190°, the product did contain a carbazole as evidenced by the production of a stable blue-green colour when its solution in sulphuric acid was treated with sodium nitrite. The carbazole could not however be obtained pure, and was isolated from the mixture as its N-acetyl derivative (IV). Hydrolysis of the amide (IV) gave a gum which could not be induced to crystallize. Its ultra-violet spectrum and colour reactions were typical of a carbazole, and leave no doubt as to the correctness of structure (IV) for the acetyl compound.

EXPERIMENTAL

3-Bromo-2-nitrotrifluoromethylbenzene

A warm solution of 3-amino-2-nitrotrifluoromethylbenzene (10 g) in conc H_2SO_4 (40 cc) and water (36 cc) was cooled rapidly with vigorous stirring. The fine suspension of amine sulphate so produced was treated with a solution of sodium nitrite (4·0 g) in water (10 cc) at 0°. After being stirred for 20 min the diazo-solution was poured into a cold mixture of cuprous bromide (7·0 g) and 48% hydrobromic acid (10·0 cc). After 15 min, the mixture was boiled for 5 min and then steam distilled. From the distillate *3-bromo-2-nitrotrifluoromethylbenzene* was isolated as a pale-yellow solid (8·5 g, 70%), m.p. 29–30°, b.p. 138–140°/14 mm (Found: C, 31·3; H, 1·3. $C_7H_2O_2NF_3Br$ requires: C, 31·1; H, 1·1%).

2-Nitro-3-trifluoromethyldiphenylamine

(a) A mixture of 3-bromo-2-nitrotrifluoromethylbenzene (1·0 g), freshly-distilled aniline (3·0 g), anhydrous potassium carbonate (1·0 g) and a trace of cuprous bromide was heated under reflux at 200–210° for 20 hr. After removing excess aniline in steam, the residue was extracted several times with ether. The combined extracts were dried and evaporated to yield a solid, which crystallized from aqueous ethanol. *2-Nitro-3-trifluoromethyldiphenylamine* was thereby obtained in lustrous orange-red needles (0·2 g, 19%), m.p. 100–101° (Found; C, 55·0; H, 3·1; F, 20·4. $C_{13}H_9O_2NF_3$ requires: C, 55·3; H, 3·2; F, 20·2%).

(b) A mixture of 3-amino-2-nitrotrifluoromethylbenzene (9·0 g), bromobenzene (30 cc), anhydrous potassium carbonate (2·0 g) and cuprous iodide (0·5 g) was heated under reflux with stirring for 18 hr. Excess bromobenzene was distilled off in steam, and the residue was poured into water. The precipitate was collected and extracted with boiling ethanol. A little water was added to the extract, which on cooling afforded long red needles (6·3 g, 52%), m.p. 101–102° undepressed on admixture with a sample prepared by method (a).

2-Amino-3-trifluoromethyldiphenylamine

A solution of 2-nitro-3-trifluoromethyldiphenylamine (0·75 g) in ethanol (15·0 cc) was hydrogenated at room temp and press using Raney nickel catalyst (ca. 0·5 g). When the uptake of hydrogen was complete (ca. 1·5 hr), the solution was filtered and evaporated under reduced pressure. The residual solid was recrystallized from aqueous ethanol to give long colourless needles of *2-amino-3-trifluoromethyldiphenylamine* (0·62 g, 92%), m.p. 79–80° (Found: C, 61·7; H, 3·8. $C_{13}H_{11}N_2F_3$ requires: C, 61·9; H, 4·3%).

1-Phenyl-4-trifluoromethylbenzotriazole

A fine suspension of 2-amino-3-trifluoromethyldiphenylamine hydrochloride (from 0·34 g amine) in 2 N HCl (12 cc) was stirred and treated with a solution of sodium nitrite (0·065 g) in water (2 cc),

the mixture being kept below 5°. After the mixture had been stirred for a further 15 min, the solid was collected and recrystallized from aqueous ethanol. *1-Phenyl-4-trifluoromethylbenzotriazole* (0·28 g, 79%) was thereby obtained in colourless plates, m.p. 152–153° (Found: C, 59·0; H, 2·8; F, 21·5. $C_{13}H_8N_3F_3$ requires: C, 59·3; H, 3·0; F, 21·7%).

The decomposition of 1-*phenyl-4-trifluoromethylbenzotriazole*

An intimate mixture of the triazole (0·5 g) and *m*-dinitrobenzene (0·5 g) was heated in an oil-bath for 1 hr at 300°. From the dark reaction mixture starting material (0·4 g) was recovered.

When equal weights of the triazole and either copper bronze or calcium oxide were heated together at 350° for 15 min extensive decomposition occurred. No triazole or carbazole was isolated from the reaction.

2-Nitro-5-trifluoromethyldiphenylamine

A mixture of 3-amino-4-nitrotrifluoromethylbenzene (4·5 g), bromobenzene (15 cc), potassium carbonate (1·0 g) and cuprous iodide (0·5 g) was stirred and boiled under reflux for 15 hr. Excess bromobenzene was removed by steam distillation, and the residue was cooled and diluted with water. The precipitate was collected at the pump, washed with water, dried *in vacuo* and extracted with boiling ethanol (15 cc). The extract was filtered, and the hot filtrate was diluted with water. On cooling the mixture afforded orange-yellow needles (4·3 g, 67%) of *2-nitro-5-trifluoromethyldiphenylamine* m.p. 79° (Found: C, 55·8; H, 3·4; F, 20·0. $C_{13}H_9O_2N_2F_3$ requires: C, 55·3; H, 3·2; F, 20·2%).

2-Amino-5-trifluoromethyldiphenylamine

A solution of 2-nitro-5-trifluoromethyldiphenylamine (5·0 g) in ethanol (45 cc) was shaken under hydrogen at room temp and press with Raney nickel (ca. 2·5 g). When hydrogen uptake was complete (ca. 1·5 hr) the solution was filtered and evaporated. The residue, which soon solidified, was taken up in light petroleum (b.p. 60–80°). On cooling the solution deposited colourless needles (4·0 g) of *2-amino-5-trifluoromethyldiphenylamine* m.p. 59° (Found: C, 61·8; H, 4·3; F, 22·3. $C_{13}H_{11}N_2F_3$ requires: C, 61·9; H, 4·3; F, 22·6%).

1-Phenyl-6-trifluoromethylbenzotriazole

A fine suspension of 2-amino-5-trifluoromethyldiphenylamine hydrochloride (from 0·34 g amine) in a mixture of 2 N HCl (6 cc) and glacial acetic acid (5 cc) was treated at 0–5° with a solution of sodium nitrite (0·065 g) in water (2 cc) with stirring. After being stirred for a further 15 min at 0°, the mixture was diluted with water (10 cc) and filtered. The solid was dried *in vacuo* and recrystallized from light petroleum (b.p. 60–80°). *1-Phenyl-6-trifluoromethylbenzotriazole* was thereby obtained in colourless prisms (0.18 g 58%), m.p. 92–93° (Found: C, 59·3; H, 3·3. $C_{13}H_8N_3F_3$ requires: C, 59·3; H, 3·0%).

The decomposition of the triazole was attempted under the same conditions as for the 4-trifluoromethyl isomer. The results were essentially the same as those for that isomer.

2-Nitro-4-trifluoromethyldiphenyl

A mixture of 4-amino-3-nitrotrifluoromethylbenzene[7] (12·0 g), conc H_2SO_4 (12 cc) and water (10 cc) was vigorously stirred at 0° and treated with a solution of sodium nitrite (4·7 g) in water (10 cc). Stirring was continued for a further 30 min at 0°. The diazo-solution was then filtered and mixed with benzene (150 cc). A solution of hydrated sodium acetate (75 g) in water (170 cc) was then added dropwise to the vigorously stirred mixture whilst the temp was kept below 5°. After the mixture had been stirred for a further 2 hr at this temp, it was shaken for 96 hr. The benzene layer was then separated and the aqueous layer extracted with ether (2 × 125 cc). The combined organic layers were dried and distilled to yield a liquid (4·2 g), b.p. 144–146°/5 mm, which was dissolved in light petroleum (b.p. 60–80°) and chromatographed on neutral alumina (3 × 30 mm). Elution with the same solvent afforded the first fraction as a yellow oil (3·45 g), b.p. 125–127°/0·5 mm, which solidified. Recrystallization from aqueous ethanol afforded *2-nitro-4-trifluoromethyldiphenyl* (3·4 g, 22%) in long yellow needles, m.p. 45–46° (Found: C, 58·4; H, 3·2; F, 21·3. $C_{13}H_8O_2NF_3$ requires: C, 58·4; H, 3·0; F, 21·3%).

2-Amino-4-trifluoromethyldiphenyl

A solution of 2-nitro-4-trifluoromethyldiphenyl (1·0 g) in methanol (20 cc) was shaken under hydrogen at room temp and press with Raney nickel (ca. 0·5 g). When hydrogen uptake was complete (ca. 1 hr), the solution was filtered and evaporated to dryness. The solid residue was recrystallized from aqueous ethanol to afford *2-amino-4-trifluoromethyldiphenyl* in colourless leaflets (0·8 g), m.p. 48–49° (Found: C, 65·9; H, 4·3; F, 23·8. $C_{13}H_{10}NF_3$ requires: C, 65·8; H, 4·2; F, 24·0%.)

2-Trifluoromethylcarbazole

A stirred solution of 2-amino-4-trifluoromethyldiphenyl (0·3 g) in glacial acetic acid (1 cc) and conc H_2SO_4 (2 cc) was kept at 5° during the dropwise addition of the solution of sodium nitrite (0·1 g) in water (2 cc). The solution was stirred for a further 20 min, filtered and treated with urea. The diazo-solution was then diluted with water (40 cc), cooled in ice and treated with a solution of sodium azide (0·1 g) in water (5 cc). The turbid mixture was stirred for a further 30 min at 0° and then set aside overnight. Next morning the mixture was neutralized with N-potassium carbonate and extracted with ether (2 × 25 cc). The combined extracts were dried and evaporated to give 2-azido-4-trifluoromethyldiphenyl (0·3 g, 90%) as an oil, which was not purified further.

A solution of the azide (0·2 g) in pure tetralin (10 cc) was irradiated in a quartz vessel with a mercury vapour lamp. After a short induction period nitrogen was evolved. When the evolution of nitrogen had ceased (ca. 2·5 hr) the solution was evaporated at 70°/3 mm to ca. 3 cc. The residue, when treated at 0° with light petroleum–benzene mixture, afforded a colourless solid which was collected and washed with light petroleum. It crystallized from benzene to afford colourless leaflets of 2-trifluoromethylcarbazole (0·08 g, 45%), m.p. 209–210°, undepressed on admixture with a sample prepared by the Fischer–indole method. The infra-red spectrum of the two samples were identical.

2-Nitro-2′-trifluoromethyldiphenyl

Activated copper bronze (15 g) was added in small portions with stirring to a mixture of *o*-iodotrifluoromethylbenzene[8] (14 g) and *o*-bromonitrobenzene (10 g) at 150°. A condenser was then attached to the flask and the temp was raised successively to 220° for 30 min and to 270° for 30 min. The cooled mixture was pulverized and extracted with boiling ether (2 × 150 cc). The combined extracts were treated with charcoal and evaporated to afford a gum, which was taken up in boiling light petroleum, (b.p. 60–80). On cooling the solution deposited a solid which, on recrystallization from ethanol, afforded yellow needles (1·4 g) of 2,2′-dinitrodiphenyl, m.p. 122–123°.

The ethanolic filtrate was evaporated to a solid residue, which, on boiling with light petroleum, afforded an undissolved residue of 2,2′-dinitrodiphenyl (0·8 g). When the solution was evaporated to dryness it afforded a solid residue 'A' (0·4 g), m.p. 74–76°.

When the first light petroleum filtrate was evaporated to ca. 10 cc and kept overnight it afforded a solid which after recrystallization from ethanol was obtained as yellow needles, 'B', (1·8 g), m.p. 76–78°.

Solids 'A' and 'B' were combined, dissolved in a mixture of benzene–light petroleum (b.p. 60–80°) (4 : 1) and chromatographed on alumina (2 × 10 cm). Elution with the same solvent (200 cc) afforded a solid which crystallized from aqueous ethanol. *2-Nitro-2-trifluoromethyldiphenyl* was thereby obtained in long pale-yellow needles (1·7 g, 14%), m.p. 73–74° (Found: C, 58·3; H, 2·9. $C_{13}H_8O_2NF_3$ requires: C, 58·4; H, 3·0%).

The residue and filtrates which presumably contained 2,2′-bistrifluoromethyldiphenyl were not examined further.

2-Amino-2′-trifluoromethyldiphenyl

2-Trifluoromethyl-2′-nitrodiphenyl (0·2 g) in ethanol (15 cc) was hydrogenated at room temp and press with 7% palladized charcoal (0·1 g) as catalyst. When hydrogen uptake was completed (ca. 30 min) the solution was filtered and evaporated to dryness. The residual solid was recrystallized from light petroleum (b.p. 40–60°) to give *2-amino-2′-trifluoromethyldiphenyl* as colourless needles (0·17 g), m.p. 47–48° (Found: C, 66·0; H, 4·3; F, 24·0. $C_{13}H_{10}NF_3$ requires: C, 65·8; H, 4·2; F, 24·0%).

[8] R. G. Jones, *J. Amer. Chem. Soc.* **69**, 2346 (1947).

N-Acetyl-4-trifluoromethylcarbazole

A cold solution of sodium nitrite (0·1 g) in water (2 cc) was added dropwise with stirring to a solution of 2-amino-2′-trifluoromethyl-diphenyl (0·3 g) in glacial acetic acid (1 cc) and conc H_2SO_4 (2 cc). Stirring was continued for a further 30 min, when the diazo-solution was filtered, treated with urea and diluted with water (40 cc). A solution of sodium azide (0·15 g) in water (2 cc), was then added to the diazo-solution at 0°. After 2 hr at room temp the mixture was extracted with ether (2 × 50 cc). The combined ethereal extracts were dried and evaporated to give 2-azido-2′-trifluoromethyldiphenyl as a gum (0·2 g, 60%) which was not purified further.

When the azide was decomposed by ultra-violet light in the manner described for the other isomer nitrogen was evolved. No carbazole could be isolated from the product and colour reactions failed to detect any carbazole in the product.

A solution of the azide (0·2 g) in pure decalin (5 cc) was added dropwise to decalin (25 cc) at 180–190° (internal temp). A vigorous evolution of nitrogen ensued and heating was continued 2–3 min after the addition was complete. Removal of the solvent under reduced press afforded a gum which could not be obtained solid, but which gave a bluish-green colour when its solution in conc H_2SO_4 was treated with HNO_3. A solution of the gum in acetic anhydride (4 cc) and 60% perchloric acid (1 drop) was maintained at 75° for 1 hr and then poured into water. The mixture was extracted with ether (2 × 25 cc) and the combined extracts were dried. Removal of the solvent afforded a gum which was taken up in a mixture of benzene and light petroleum (b.p. 60–80°) (20 : 1) and chromatographed on alumina (1 × 12 cm). Elution with the same solvent gave a solid which crystallized from aqueous ethanol in colourless leaflets of N-*acetyl-4-trifluoromethylcarbazole* (0·03 g, 17%), m.p. 94–95° (Found: C, 64·6; H, 3·9; F, 20·4. $C_{15}H_{10}ONF_3$ requires: C, 65·0; H, 3·6; F, 20·6%). Light absorption: λ_{max} 261, 292 and 320 mμ; log ϵ_{max} 4·09, 4·16 and 3·78.

When the N-acetyl compound was heated at 70° for 1 hr with aqueous ethanolic potassium hydroxide, it afforded a gum which could not be obtained crystalline. Its solution in conc H_2SO_4 gave a deep bluish-green colour when treated with a trace of conc HNO_3. Light absorption in ethanol: λ_{max} 235, 245, 260, 300, 320 and 330 mμ; log ϵ_{max} 3·60, 3·57, 3·56, 3·5, 3·41 and 3·41 respectively.

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THE SYNTHESES OF 2- AND 4-TRIFLUOROMETHYL-CARBAZOLES VIA DIPHENYLAMINES

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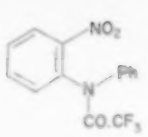
Abstract—Carbazoles, unsubstituted in the 9-position, have been prepared by applying the Pschorr reaction to N-acetyl-2-aminodiphenylamines. When applied to the preparation of carbazole itself and 2-trifluoromethylcarbazole the reaction was straightforward. When applied to the formation of 4-trifluoromethylcarbazole, the reaction gave the carbazole or the corresponding triazole or benziminazole depending upon the conditions used. It has been shown that the benziminazole can be formed by incorporating *one* of the nitrogen atoms of the diazonium intermediate into the heterocyclic ring. A mechanism is proposed for this novel reaction. 3-Trifluoromethyldiphenylamine has been prepared by standard methods.

N-ALKYL carbazoles can be made from N-alkyl *o*-aminodiphenyl amines by an application of the Pschorr reaction.[1,2] For the preparation of carbazoles unsubstituted on the nitrogen atom it is necessary to protect this atom with a group which obviously should be easily removable at the end of the synthesis. If no protecting group is employed the reaction leads to the formation of benzotriazoles. Using the acetyl group to protect the nitrogen during the formation of the carbazole system we have made 2- and 4-trifluoromethylcarbazole and carbazole itself.

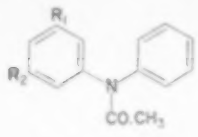
The easy hydrolysis of the N-trifluoroacetyl group has made it a useful protecting group in peptide synthesis,[3] and our first experiments were concerned with the use of this group. For the synthesis of carbazole itself, the intermediate N-trifluoroacetyl-2-nitrodiphenylamine (I) was made by warming the diphenylamine with trifluoroacetic anhydride without the use of a catalyst. The N-trifluoroacetyl derivative (I) could not however be reduced catalytically to the amine. Presumably a combination of the bulky phenyl and trifluoroacetyl groups prevents access of the catalyst to the nitro-group. Most useful chemical reductions are precluded since the conditions employed would lead to the hydrolysis of the N-trifluoroacetyl group.

It has been shown that N-acetyl carbazoles can be smoothly deacetylated with acid, alkali[4] or even lithium aluminium hydride.[5] Accordingly the acetyl group was employed as a blocking group in further experiments, the synthesis of carbazole itself used as a model. In contrast to the N-trifluoroacetyl derivative, N-acetyl-2-nitrodiphenylamine could easily be catalytically reduced to the amine. When N-acetyl-2-aminodiphenylamine was diazotized and the diazo-solution rendered alkaline,[1] N-acetyl carbazole could be isolated therefrom in a satisfactory yield (45 per cent) for this type of reaction.

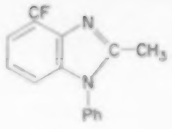
[1] F. R. Storrie and S. H. Tucker, *J. Chem. Soc.* 2255 (1931).
[2] D. H. Hey and R. D. Mulley, *J. Chem. Soc.* 2276 (1952).
[3] F. Weygand and M. Reiher, *Chem. Ber.* **88**, 26 (1955).
[4] J. E. Saxton, *J. Chem. Soc.* 3593 (1952).
[5] V. M. Mićović and M. LJ. Mihailović, *J. Org. Chem.* **18**, 1190 (1953).



I



II : R_1 = H, R_2 = CF_3
III : R_1 = CF_3, R_2 = H



IV

For the synthesis of 2-trifluoromethyl carbazole we required the intermediate N-acetyl-2-amino-5-trifluoromethyldiphenylamine (II). This was prepared from 2-nitro-5-trifluoromethyldiphenylamine[6] by acetylating it with acetic anhydride in the presence of perchloric acid or zinc chloride and then reducing the nitro-group catalytically. The amine (II) was unstable and no attempt was made at purification. It was diazotized in a mixture of glacial acetic acid and dilute sulphuric acid, and the diazo-solution was warmed at 50–60° to complete the reaction. These conditions were somewhat limiting and were in fact worked out for the other trifluoromethyl isomer as will be described later. In the present instance they afforded N-acetyl-2-trifluoromethylcarbazole in 27 per cent yield. A comparison between this compound and that obtained by acetylating the carbazole which had been made from *m*-trifluorophenylhydrazine showed that they were identical.

N-Acetyl-2-amino-3-trifluoromethyldiphenylamine (III), the amine required for the preparation of 4-trifluoromethylcarbazole, was obtained from 2-nitro-3-trifluoromethyldiphenylamine by acetylation followed by reduction of the nitro-group. Attempts to convert the amine (III) into 4-trifluoromethylcarbazole were not immediately successful.

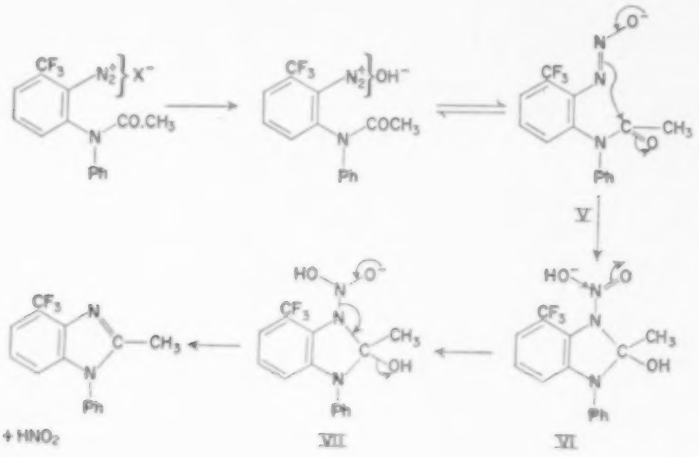
When the amine (III) was diazotized under normal conditions and the resulting solution treated with alkali, there was obtained an excellent yield of 2-methyl-1-phenyl-4-trifluoromethylbenziminazole (IV), whose structure was assigned from the following considerations. It analysed for $C_{15}H_{13}N_2F_3$ it was basic and formed stable salts with mineral acids. Its infra-red spectrum contained no band attributable to a carbonyl group, but a strong band at 1600 cm^{-1} could be assigned to a C=N group. In addition bands at 700 and 760 cm^{-1} served to indicate a mono-substituted phenyl group. Its ultra-violet spectrum differed significantly from those of carbazoles, but resembled that of benziminazole itself.[7] The formation of benziminazoles from acyldiphenylamines under acid conditions has been noted previously[8] and suggested that our compound had arisen during the dissolution of the diphenylamine in acid prior to diazotization. This was shown to be the case when the experiment was repeated without the intervention of sodium nitrite. The benziminazole was again obtained when the diazotization was attempted with nitrosyl sulphuric acid in glacial acetic acid. In this experiment the temperature was kept below 10° at all times. The ready formation of benziminazoles at room temperature is notable. In further experiments the temperature was kept below 20° and only dilute mineral acids were used.

When the diazotization was carried out in glacial acetic acid in the presence of N-sulphuric acid an orange colouration was produced in the solution. That diazotization had in fact taken place was confirmed with alkaline β-naphthol. After the

[6] Preceding Paper.
[7] K. Hofmann, *Imidazole and Its Derivatives* Part I, p. 253. Interscience, New York (1953).
[8] M. A. Philips, *J. Chem. Soc.* 2820 (1929).

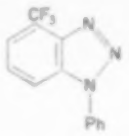
diazo-solution had been rendered alkaline, the benziminazole (IV) was again obtained. The yield (48 per cent) of benziminazole was surprisingly high and seemed to indicate that at least some of it must have been formed from the diazonium compound. This view was confirmed when the diazotized amine was coupled with β-naphthol. From a control experiment the azo-dye was obtained in 60 per cent yield of analytical purity, so that the yield of diazo-compound must have been much higher.

The formation of an iminazole ring from the diazo-compound signifies that one of its nitrogen atoms has been incorporated into the heterocyclic ring. This rupture of the diazo-linkage appears to have no parallel in the literature. The annexed scheme gives a possible mechanism for this novel reaction.



On the addition of alkali the diazonium salt is converted successively into hydroxide and then diazotate, which can ionize to give V. The proximity of the acetyl group, coupled with the ease with which it can undergo nucleophilic attack when attached to a weakly basic nitrogen atom, makes ring closure a favourable process. The acquisition of a proton then gives the intermediate VI. Attack by hydroxide ion, followed by the electronic shifts indicated in structure VII, complete the process. The resulting increase in aromaticity will provide the necessary driving force for the latter stages. That carbazole formation, the normal reaction, does not occur in this case may be ascribed to the *ortho*-trifluoromethyl group which will sterically hinder the formation of the transition state for carbazole formation much more so than that for the ring closure reaction. This steric effect is not pertinent to the formation of carbazole itself or the other trifluoromethyl isomer and no benziminazoles were encountered in their preparation. The formation of benziminazoles by the above mechanism implies that if the decomposition of the diazonium compound were carried out in acid solution no benziminazole would be formed. This indeed proved to be the case when the acid diazo solution was merely warmed to effect its decomposition. No basic material was formed in the reaction, from which 4-trifluoromethyl carbazole was isolated in 25 per cent yield. In an attempt to increase the yield of carbazole, the diazo-solution from amine (III) was made more strongly acidic by the addition of concentrated sulphuric acid before heating it. The sole product from this reaction

was 1-phenyl-4-trifluoromethyl triazole (VIII). Here the removal of the acetyl group may well take place after ring-closure has occurred.



VIII

Amides can behave as nucleophiles and this is well illustrated in our final experiment which was designed to eliminate the possibility, still present when we made this sample of 4-trifluoromethylcarbazole, that the material we had obtained was 3-trifluoromethyldiphenylamine and not the carbazole. The former compound was synthesized by condensing *m*-acetylaminotrifluoromethylbenzene with bromobenzene. Here the nucleophilic amide group displaces bromide ion an energetically less favourable reaction than triazole formation mentioned above, albeit under more strenuous reaction conditions. The infra-red spectrum of N-acetyl-3-trifluoromethyldiphenylamine shows bands at 707, 767 and 814 cm^{-1} which can be assigned to mono- and *meta*-substituted benzene rings. A band at 1695 cm^{-1} can be assigned to the amide group: this high frequency seems general for amides of weakly or non-basic amines and is found also for N-acetylcarbazoles. It is in the ultra-violet region that spectral differences are most striking. N-Acetyl-3-trifluoromethyldiphenylamine shows only a single band at 240 mμ and the diphenylamine itself a single band at 285 mμ. These contrast sharply with the complex spectra of the carbazoles and their N-acetyl derivatives. The benziminazole (IV) and triazole (VIII) spectra are again characteristic for these types of compound[7,9] and show marked differences when compared with those of carbazoles and diphenylamines.

EXPERIMENTAL

N-Trifluoroacetyl-2-nitrodiphenylamine

When 2-nitrodiphenylamine (1·5 g) was added to trifluoroacetic anhydride (10 g) a mild exothermic reaction ensued. When the reaction had subsided the mixture was boiled under reflux for 10 min and then evaporated under reduced press. The residual solid was recrystallized from aqueous ethanol to afford N-*trifluoroacetyl-2-nitrodiphenylamine* (1·55 g, 71%) in leaflets, m.p. 112° (Found: C, 54·3; H, 3·0. $C_{14}H_9O_3N_2F_3$ requires: C, 54·2; H, 2·9%).

N-Acetyl-2-aminodiphenylamine

N-acetyl-2-nitro-diphenylamine was made by warming the diphenylamine with acetic anhydride in the presence of zinc chloride. A solution of the N-acetyl compound (1·0 g) in ethanol (20 cc) was shaken under hydrogen at room temp and press with Raney nickel (ca. 0·5 g). When hydrogen uptake had ceased (ca. 1·5 hr), the solution was filtered and evaporated to dryness. The residual solid was recrystallized from aqueous ethanol to afford N-*acetyl-2-aminodiphenylamine* as colourless leaflets (0·8 g), m.p. 115–116° (Found: C, 74·3; H, 5·9. $C_{14}H_{14}ON_2$ requires: C, 74·1; H, 6·2%). Its hydrochloride had m.p. 210–211° after recrystallization from ether–ethanol.

The *picrate* crystallized with difficulty from amyl alcohol in small yellow needles, m.p. 222–223° (decomp) (Found: C, 56·2; H, 3·4. $C_{20}H_{17}ON_5$ requires: C, 56·6; H, 3·4%).

N-Acetylcarbazole

A solution of N-acetyl-2-aminodiphenylamine hydrochloride (2·0 g) in conc HCl (10 cc) at 0° was treated with a solution of sodium nitrite (0·6 g) in water (3 cc). The mixture was stirred for

[9] Mme. Ramart-Lucas and J. Hoch, *Bull. Soc. Chim. Fr.* [5], **16**, 447 (1949).

15 min after the addition of the nitrite solution and then rendered alkaline by the rapid addition of 4 N-KOH, when a dark-coloured solid separated almost immediately. The solid was collected, dried *in vacuo* and then boiled in ether with charcoal. The filtered solution was evaporated to afford a residue which crystallized from benzene–light petroleum (b.p. 40–60°). Recrystallization from light-petroleum (b.p. 40–60°) afforded colourless needles (0·75 g, 45%) of N-acetylcarbazole, m.p. 69–70°, undepressed on admixture with an authentic specimen.

N-*Acetyl-2-nitro-5-trifluoromethyldiphenylamine*

A solution of 5-trifluoromethyl-2-nitrodiphenylamine (1·5 g)[6] in acetic anhydride (10 cc) containing 60% perchloric acid (1 drop) was maintained at 50° for 1 min. During this time the colour of the solution changed from orange-red to pale yellow. On pouring the solution into ice-cold water (50 cc) a precipitate was formed. The solid was collected at the pump, washed with aqueous potassium carbonate, then with water and dried *in vacuo*. Recrystallization from ether–light petroleum (b.p. 40–60°), followed by recrystallization from light petroleum (b.p. 40–60°) afforded N-*acetyl-2-nitro-5-trifluoromethyldiphenylamine* as pale-yellow prisms (1·5 g, 87%), m.p. 62–63° (Found: C, 55·8; H, 3·4; F, 17·4. $C_{15}H_{11}O_3N_2F_3$ requires: C, 55·6; H, 3·4; F, 17·6%).

When the diphenylamine (0·2 g) in acetic anhydride (5 cc) containing a trace of zinc chloride was warmed at 70–75° for 5 min, and the product worked up as described above, the N-acetyl compound was obtained in 78% yield.

N-*Acetyl-2-amino-5-trifluoromethyldiphenylamine*

A solution of N-acetyl-2-nitro-5-trifluoromethyldiphenylamine (0·2 g) in ethanol (15 cc) was shaken under hydrogen at room temp and press with 8% palladized charcoal (0·1 g). When hydrogen uptake was complete (ca. 2 hr) the solution was filtered and evaporated to dryness to give the amine as a colourless solid (0·16 g), m.p. 63–65°. The amine could not be recrystallized and was used in subsequent reactions without further purification.

N-*Acetyl-2-trifluoromethylcarbazole*

Ice-cold N H_2SO_4 (1 cc) was added to a cooled solution of N-acetyl-2-amino-5-trifluoromethyldiphenylamine (0·16 g) in glacial acetic acid (2 cc). Whilst the temp was kept below 5°, this solution was treated with sodium nitrite (0·08 g) in water (2 cc). After being stirred for 15 min the solution was warmed at 50–60° for 15 min. A copious evolution of nitrogen accompanied the separation of an oil. Water (40 cc) was then added to the mixture which was set aside at room temp for 2 hr. The aqueous layer was decanted and the residual oil taken up in ether (25 cc). The ethereal extract was washed with N Na_2CO_3, dried and evaporated. The residual gum (0·16 g) was taken up in benzene–light petroleum (1 : 10) and chromatographed on neutral alumina (15 × 1 cm). Elution with benzene–light petroleum (1 : 20) afforded a solid which crystallized from light petroleum (b.p. 60–80°). N-Acetyl-2-trifluoromethylcarbazole was thereby obtained in small prisms (0·025 g, 27%), m.p. 122–123°, undepressed on admixture with an authentic specimen.[6] The infra-red spectra show a carbonyl band at 1716 cm^{-1} (KBr disk), and are otherwise identical.

N-*Acetyl-2-nitro-3-trifluoromethyldiphenylamine*

2-Nitro-3-trifluoromethyldiphenylamine (1·5 g),[6] acetic anhydride (10 cc) and a small piece of anhydrous zinc chloride were maintained at 60–70° for 20 min. The mixture was then poured into water and extracted with ether (3 × 25 cc). The combined extracts were washed with aqueous sodium carbonate, dried, treated with charcoal and evaporated. Recrystallization of the residual solid from ethanol afforded long pale-yellow needles of N-*acetyl-2-nitro-3-trifluoromethyldiphenylamine* (1·5 g), m.p. 96–97° (Found: C, 55·8; H, 3·6. $C_{15}H_{11}O_3N_2F_3$ requires: C, 55·6; H, 3·4%).

N-*Acetyl-2-amino-3-trifluoromethyldiphenylamine*

A solution of N-acetyl-2-nitro-3-trifluoromethyldiphenylamine (1·4 g) in ethanol (25 cc) was shaken under hydrogen at room temp and press with Raney nickel. When hydrogen uptake was complete (2·5 hr) the solution was filtered and evaporated. When the residual solid was recrystallized

from ethanol N-*acetyl*-2-*amino*-3-*trifluoromethyldiphenylamine* was obtained in colourless prisms (0·8 g), m.p. 153–154° (Found: C, 60·9; H, 4·2. $C_{15}H_{12}ON_2F_3$ requires: C, 61·2; H, 4·4%).

2-Methyl-1-phenyl-4-trifluoromethylbenziminazole

A mixture of N-acetyl-2-amino-3-trifluoromethyldiphenylamine (0·2 g), conc HCl (2 cc) and water (2 cc) was heated at 75–80° for 2–3 min. The cooled solution was poured into water (20 cc) and rendered alkaline by the addition of 4 N KOH. The precipitated solid was collected at the pump, washed with water, dried *in vacuo* and recrystallized from light petroleum (b.p. 80–100°). *2-Methyl-1-phenyl-4-trifluoromethylbenziminazole* was thus obtained in colourless glistening plates (0·14 g), m.p. 143° (Found: C, 64·7; H, 3·7; F, 20·5. $C_{15}H_{11}N_2F_3$ requires : C, 65·2; H, 4·0; F, 20·7%).

The infra-red spectrum (KBr disc) shows bands at 1600 (C=N stretching), 700 and 760 (mono-substituted benzene ring) cm^{-1}. Light absorption in ethanol: λ_{max} 240, 256, 279 and 287 mμ; log ϵ 3·9, 3·94, 3·86 and 3·85 respectively.

The *hydrochloride*, obtained by treating an ethereal solution of the base with hydrogen chloride, crystallized from ethanol–ether in colourless leaflets, m.p. 215° (decomp) (Found: C, 57·5; H, 4·0. $C_{15}H_{12}N_2F_3Cl$ requires: C, 57·6; H, 3·8%).

Diazotization of N-*acetyl*-2-*amino*-3-*trifluoromethyldiphenylamine*

(a) A solution of the amine (0·2 g) in glacial acetic acid (2 cc) was cooled rapidly to below 5°. Ice-cold 2 N H_2SO_4 (2 cc) was then added dropwise to the solution, followed immediately by a cold solution of sodium nitrite (0·08 g) in water (2 cc), when the colour of the solution deepened. After standing for 15 min at 0°, the solution was rendered alkaline by the addition of 4 N KOH, the temp being kept below 10°. A solid separated from the mixture which was stirred for 15 min and extracted with ether (3 × 25 cc). The combined extracts were dried and evaporated. The residual solid was taken up in a mixture of benzene and light petroleum (b.p. 60–80°) (2 : 5) and chromatographed on neutral alumina (10 × 1 cm). Elution with benzene afforded 2-methyl-1-phenyl-4-trifluoromethyl-benziminazole, obtained as colourless prisms (0·06 g, 48%) from light petroleum (b.p. 60–80°), m.p. 143° undepressed on admixture with an authentic specimen.

(b) After the amine (0·1 g) had been diazotized as described in (a), the diazo-solution was added dropwise to a solution of β-napththol (0·2 g) in 4 N KOH (20 cc) at 5°. After the mixture had stood for 15 min, the deep-red solid was collected at the pump, washed with water and dried *in vacuo*. It was then taken up in benzene and chromatographed on neutral alumina (20 × 1 cm). Elution with the same solvent afforded N-*acetyl*-2-(1-*azo*-2-*naphthol*)-3-*trifluoromethyldiphenylamine*, which crystallized from aqueous methanol in small deep-red needles (0·09 g, 60%), m.p. 152–153° (Found: C, 66·8; H, 4·2; F, 12·4. $C_{25}H_{18}O_2N_3F_3$ requires: C, 66·8; H, 4·0; F, 12·7%).

(c) Ice-cold N H_2SO_4 (2 cc) was added dropwise to a solution of the amine (0·5 g) in glacial acetic acid (8 cc). On the addition of a solution of sodium nitrite (0·2 g) in water (2 cc) the mixture assumed an orange-yellow colour and gave a precipitate with alkaline β-naphthol. After being stirred for 20 min, the solution was treated with conc H_2SO_4 (3 cc) and stirred for a further 10 min. The mixture was then heated at 50–60° for 45 min when a colourless precipitate was formed. After being diluted to 50 cc with water, the mixture was left in a refrigerator for 24 hr. The solid was then collected at the pump, washed with water and dried. Recrystallization from aqueous acetic acid afforded 1-phenyl-4-trifluoromethylbenzotriazole in colourless leaflets (0·17 g, 38%), m.p. 152–153° undepressed on admixture with an authentic specimen.[6] Light absorption in ethanol: λ_{max} 272 mμ, log ϵ 3·94.

The filtrate, obtained after removing the benzotriazole, was rendered alkaline with aqueous potassium hydroxide. The precipitated solid was collected and dried. Recrystallization from light petroleum afforded colourless prisms (0·31 g) of 2-methyl-1-phenyl-4-trifluoromethylbenziminazole, m.p. 143°, undepressed on admixture with an authentic specimen.[6]

(d) A solution of the amine (0·25 g) in glacial acetic acid (5 cc) was cooled to 5° and treated dropwise with ice-cold N H_2SO_4 (2 cc) followed by a solution of sodium nitrite (0·12 g) in water (3 cc). The yellow diazo-solution was stirred for 15 min at 0° and then warmed on a water-bath at 60–70° for 30 min, whilst nitrogen was evolved. After being stored in ice for several hours the solution was filtered. The residue was dried, taken up in a mixture of benzene and light petroleum (b.p. 60–80°) (1 : 1), and chromatographed on neutral alumina (15 × 1 cm). Elution with benzene–light petroleum (20 : 1) then afforded N-acetyl-4-trifluoromethylcarbazole as colourless leaflets

(0·035 g, 29%) after recrystallization from aqueous acetic acid: m.p. 94–95°, undepressed on admixture with an authentic specimen.[6] Its solution in ethanol fluoresced strongly in ultra-violet light and showed absorption bands at λ_{max} 261, 292 and 320 mμ, log ε 4·09, 4·16 and 3·78 respectively.

N-Acetyl-3-trifluoromethyldiphenylamine

An anhydrous mixture of *m*-acetylaminotrifluoromethylbenzene (10 g), nitrobenzene (75 cc), bromobenzene (30 cc), potassium carbonate (5 g), cuprous iodide (1 g) and copper bronze (1 g) was stirred vigorously and boiled under reflux for 24 hr. The mixture was then distilled in steam and the distillate discarded. The non-volatile solid was collected at the pump and extracted with boiling ether (100 cc). Evaporation of the ethereal extract afforded a semi-solid residue, which on treatment with light petroleum (b.p. 60–80°) containing a little benzene afforded *m*-acetylaminotrifluoromethylbenzene (3 g) as a crystalline solid. The mother liquors from this operation were then evaporated and the residue therefrom was taken up in benzene–light petroleum (1 : 4) and chromatographed on neutral alumina (3 × 20 cm). Elution with benzene afforded a solid which after crystallization from light petroleum (b.p. 60–80°) gave N-*acetyl-3-trifluoromethyldiphenylamine* (4·0 g, 29%) in colourless prisms, m.p. 53–54° (Found: C, 64·6; H, 4·1. $C_{15}H_{12}ONF_3$ requires: C, 64·5; H 4·3%). Light absorption in ethanol: λ_{max} 240 mμ, log ε 4·02. The infra-red spectrum (KBr) shows bands at 1695, 814, 767 and 707 cm^{-1}.

3-Trifluoromethyldiphenylamine

A solution of N-acetyl-3-trifluoromethyldiphenylamine (0·5 g) in ethanol (10 cc) and conc HCl (10 cc) was heated under reflux for 2·5 hr. The dark-coloured liquid was then poured into water (100 cc) and the mixture extracted with ether (2 × 25 cc). The combined ethereal extracts were dried and distilled twice at 15 mm. 3-*Trifluoromethyldiphenylamine* was thereby obtained as a colourless oil (0·4 g, 95%) (Found: C, 65·7; H, 4·3; F, 24·0. $C_{13}H_{10}NF_3$ requires: C, 65·8; H, 4·2; F, 24·4%). The amine rapidly darkens in air. Light absorption in ethanol: λ_{max} 285 mμ, log ε 4·05. The infra-red (liquid film) shows a band at 3510 cm^{-1} (N—H stretching).

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ORGANOMETALLIC COMPLEXES AS CATALYSTS IN IONIC POLYMERIZATIONS*

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Abstract—The syntheses and properties of some organometallic complexes containing titanium and aluminium, which have been isolated by us in the pure state by crystallization from solvents, are here described. Whereas some of these complexes contain bridge chlorine atoms between titanium and aluminium, others do not contain halides in their molecules.

The catalytic properties exhibited by these complexes for the polymerization of ethylene and of α-olefins, are described.

Finally the nature of the co-ordinated anionic polymerizations and the causes of the stereospecificity in the polymerization of the vinyl monomers are discussed.

DURING the previous Symposium on the Chemistry of Co-ordination Compounds in Rome[1] we had given a report on the importance assumed by certain catalytic systems containing transition metals and metal–organic bonds, acting by a mechanism which has been defined by us as anionic co-ordinated.[2]

As it is known, the catalysts discovered by Ziegler belonging to that class had enabled him to prepare low-pressure linear polyethylene.[3] Working with Ziegler type catalysts, our School succeeded in discovering sterically differentiated polymers of α-olefins[4] and of diolefins.[5] Later we discovered highly stereospecific catalysts which enabled us to obtain crude polymers having a high content of crystallizable macromolecules.[6]

Several authors have given an interpretation of the mechanism of ethylene polymerizations, as well as of the stereospecific polymerizations of propylene based on the hypotheses of the structure of the catalytic complexes. These hypotheses, however, were not supported by direct, experimental proofs of the structure of the catalytic complexes. Some of these authors were only partially acquainted with our previous work.

It is, therefore, useful to report here on the structure and catalytic activity of several complexes having a well defined composition, containing titanium and aluminium, and isolated in the pure state by crystallization from solutions.

In papers already published or in press in Italian journals we describe in more detail their preparation, chemical properties and structure.

* This communication was presented in a summarized form at the International Conference on Co-ordination Chemistry held in London, April 1959.

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[2] G. Natta, *Experientia* Suppl. VII, 21 (1957).
[3] K. Ziegler, *Angew. Chem.* **67**, 426 (1955).
[4] G. Natta, P. Pino, P. Corradini, F. Danusso, G. Mazzanti, E. Mantica and G. Moraglio, *J. Amer. Chem. Soc.* **77**, 1708 (1955); G. Natta, *Atti Accad. Naz. Lincei* **4**, (8), 61 (1955); G. Natta, P. Pino and G. Mazzanti, *Chim. e Industr.* **37**, 927 (1955).
[5] G. Natta and P. Corradini, *J. Polymer Sci.* **20**, 251 (1956); G. Natta, P. Corradini and L. Porri, *Rend. Accad. Naz. Lincei* **20**, (8), 728 (1956); G. Natta, L. Porri, P. Corradini and D. Morero, *Rend. Accad. Naz. Lincei* **20**, (8), 560 (1956).
[6] G. Natta, P. Pino and G. Mazzanti, *Brevetto Ital.* 526. 101; G. Natta, P. Pino, G. Mazzanti and P. Longi, *Gazz. Chim. Ital.* **87**, 570 (1957).

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I. *Crystallizable Complexes Containing Titanium and Aluminium*

(a) *Complexes having the general formula* $(C_5H_5)_2TiCl_2AlR_1R_2$ *in which* R_1 *and* R_2 *are chlorine atoms or ethyl groups*

We have prepared three different complexes belonging to this class.[7] In Table 1 their overall formulae and physical properties are indicated. All complexes are highly

TABLE 1. PHYSICAL PROPERTIES OF COMPLEXES OF THE GENERAL FORMULA $(C_5H_5)_2TiCl_2AlR_1R_2$ WHERE R_1 AND R_2 ARE CHLORINE ATOMS OR ETHYL GROUPS)

Complex	Melting temperature (°C)	Magnetic moment B.M.
$(C_5H_5)_2TiCl_2Al(C_2H_5)_2$	126–130	1·70
$(C_5H_5)_2TiCl_2AlC_2H_5Cl$	88–92	1·57
$(C_5H_5)_2TiCl_2AlCl_2$	155–160	1·72

soluble in aromatic solvents and can be crystallized from n-heptane. The three complexes referred to above were prepared by us in two different ways:

(1) By reacting *bis*(cyclopentadienyl) titanium dichloride with an excess of aluminium alkyl compound,[7] according to the following:

$$(C_5H_5)_2TiCl_2 + Al(C_2H_5)_3 \rightarrow (C_5H_5)_2TiCl_2Al(C_2H_5)_2 + \tfrac{1}{2}C_2H_4 + \tfrac{1}{2}C_2H_6$$
$$(C_5H_5)_2TiCl_2 + Al(C_2H_5)_2Cl \rightarrow (C_5H_5)_2TiCl_2AlC_2H_5Cl + \tfrac{1}{2}C_2H_4 + \tfrac{1}{2}C_2H_6$$
$$(C_5H_5)_2TiCl_2 + AlC_2H_5Cl_2 \rightarrow (C_5H_5)_2TiCl_2AlCl_2 + \tfrac{1}{2}C_2H_4 + \tfrac{1}{2}C_2H_6$$

(2) By reacting *bis*(cyclopentadienyl) titanium monochloride respectively with diethyl-aluminium-monochloride, ethyl-aluminium-dichloride or aluminium-trichloride,[8] as follows:

$$(C_5H_5)_2TiCl + ClAl(C_2H_5)_2 \rightarrow (C_5H_5)_2TiCl_2Al(C_2H_5)_2$$
$$(C_5H_5)_2TiCl + ClAl(C_2H_5)Cl \rightarrow (C_5H_5)_2TiCl_2Al(C_2H_5)Cl$$
$$(C_5H_5)TiCl + AlCl_3 \rightarrow (C_5H_5)_2TiCl_2AlCl_2$$

The study of the chemical properties of these complexes and the X-ray examination of their lattice structure carried out on single crystals, enabled us to conclude that the two cyclopentadienyl nuclei are bound to the titanium atom, while the latter is bound to aluminium through two bridge chlorine atoms.

From all the above-mentioned complexes it is possible, by treatment with anhydrous hydrochloric acid, to recover *bis*(cyclopentadienyl) titanium dichloride[7] in high yield.

The presence of chlorine bridges, similar to those existing in other electron-deficient molecules, e.g. Al_2Cl_6 molecules, is confirmed by the reaction with trimethylamine.

If an excess of this compound is reacted, in heptane, with the complex $(C_5H_5)TiCl_2Al(C_2H_5)_2$, a precipitate is obtained which is formed by *bis*(cyclopentadienyl) titanium monochloride; after removal of the solvent by evaporation, the

[7] G. Natta, P. Pino, G. Mazzanti and U. Giannini, *J. Amer. Chem. Soc.* **79**, 2975 (1957); G. Natta, P. Pino, G. Mazzanti and U. Giannini, *La Ricerca Sci.* Suppl. **28**, (1958).

complex of trimethylamine with Al-diethyl-monochloride $(CH_3)_3N \rightarrow Al(C_2H_5)_2Cl$ can be isolated by distillation (0·5 mm Hg; 79–80°).[8]

The structure of the complex $(C_5H_5)_2TiCl_2Al(C_2H_5)_2$ has been confirmed by the determination of its crystalline structure by X-ray examination.[9] As indicated in Fig. 1, the Ti–Al distance is about 3·54 Å, the Cp–Ti–Cp angles are 130° and the Ti–Cl–Al angles are about 90°. The unit cell constants are as follows:

$$a = 15{\cdot}77 \text{ Å}; \quad b = 14{\cdot}24 \text{ Å}; \quad c = 7{\cdot}54 \text{ Å}$$

space group P_{nma}

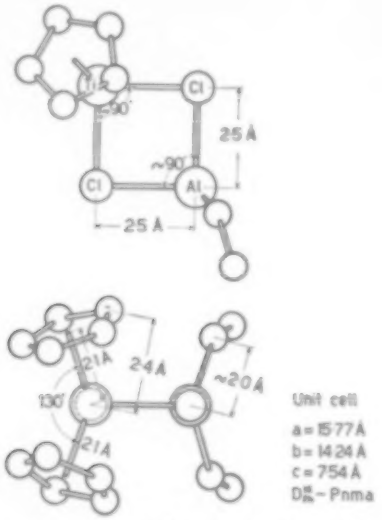

FIG. 1. Spatial model of the complex having formula: $(C_5H_5)_2TiCl_2Al(C_2H_5)_2$

X-ray investigations, for the other complexes of this class, confirm the existence of chlorine bridges in the molecule.

(b) *Complex* $[(C_5H_5)_2TiAl(C_2H_5)_2]_2$

By reacting *bis*(cyclopentadienyl) titanium monochloride in benzene at 80° with aluminium triethyl in excess, a red solid product is obtained after removal of benzene, which can be purified by crystallization from n-heptane.[10]

The purified product (tabular crystals) is very soluble in aromatic hydrocarbons, melts (dec) at 169–171° and is diamagnetic.

The results of chemical analysis and the determination of molecular weight are in agreement with the formula $[(C_5H_5)_2TiAl(C_2H_5)_2]_2$.[10]

The two cyclopentadienyl nuclei are bound to titanium. In fact, by treating an ether solution of this complex with HCl and chlorine, *bis*(cyclopentadienyl) titanium dichloride is recovered in good yields (95–97%). The X-ray examination on single crystals of this complex enabled us to establish that the molecule possesses a binary

[8] G. Natta, P. Pino, G. Mazzanti and U. Giannini, In press.
[9] G. Natta, P. Corradini and I. W. Bassi, *J. Amer. Chem. Soc.* **80**, 755 (1958).
[10] G. Natta, G. Mazzanti, P. Corradini, U. Giannini and S. Cesca, *Atti Accad. Naz. Lincei* (8), **26**, 150 (1959).

axis of symmetry and that the Ti–Ti distance is 3·07 Å, while the Ti–Al distance is 2·83 Å. The Ti–Ti–Al angle is 91°40′ and the angle between the two Ti–Ti–Al planes is 100°30′/(Fig. 2).

(c) *Complexes* $Al_2TiCl_8C_6H_5$ *and* $AlTiCl_5C_6H_5$

A solid crystalline, violet complex, containing titanium and aluminium was isolated by a Friedel–Crafts reductive reaction on $TiCl_4$. The conditions adopted were similar to those used by Fischer for the preparation of transition metal complexes, in which the metal is bound to aromatic nuclei by means of bonds of the π-type.

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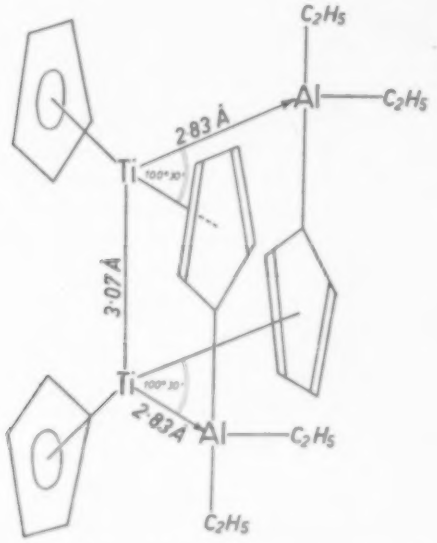


FIG. 2. Spatial model of the complex having formula: $[(C_5H_5)_2TiAl(C_2H_5)_2]_2$

When the reaction was carried out between $TiCl_4$, $AlCl_3$, Al and benzene at 80° for several hours, a complex having an overall formula $Al_2TiCl_8C_6H_5$[11] was obtained. From Table 2, it can be seen that the composition of this product does not change when varying, within rather wide limits, the ratios between the moles of the various reactants used in its preparation. This complex melts at 110–115° (dec.) and is very soluble in benzene and toluene and only slightly soluble in aliphatic hydrocarbons. It undergoes a rapid change in presence of oxygen and moisture, giving hydrochloric acid and phenol.

It reacts exothermally with water in absence of oxygen yielding benzene. This behaviour agrees with the presence of phenyl groups bound to a metal by σ bonds.

By decomposition with dilute hydrochloric acid and titration with ferric sulphate it was established that titanium is present in the trivalent form.

When treating this complex, at room temperature or lower, with compounds containing lone electron pairs, such as e.g. tetrahydrofurane, dibutyl ether, pyridine

[11] G. Natta, G. Mazzanti and F. Pregaglia, *Gazz. Chim. Ital.* In press.

or trimethylamine elimination of one molecule of $AlCl_3$ takes place. This fact might prove the presence in the complex of one $AlCl_3$ molecule linked in a labile way, in agreement with a formula of the type: $[AlTiCl_5C_6H_5]\cdot AlCl_3$.

If the reaction with tetrahydrofurane is carried out at higher temperature (50–60°C) and for longer time, the above mentioned complex undergoes considerable decomposition and, besides the tetrahydrofuranate of aluminium trichloride

TABLE 2. COMPOSITION OF THE PRODUCT OBTAINED BY REACTING $TiCl_4$, Al, $AlCl_3$ AND BENZENE, AT 80°

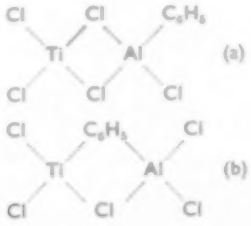
Starting reagents					Time (hr)	Product obtained			
$TiCl_4$ (moles)	$AlCl_3$ (moles)	Al (moles)	C_6H_6 (moles)	Molar ratio $Ti/AlCl_3/Al/C_6H_6$		(I) Yields %	Al %	Ti %	Cl %
0·09	0·09	0·27	1·4	1 : 1 : 3 : 15	13	60	11·77 —	10·25 —	60·65 60·60
0·06	0·06	0·12	1·2	1 : 1 : 2 : 20	6	20	11·67 11·64	10·30 10·50	60·80 —
0·09	0·117	0·180	1·8	1 : 1·3 : 2 : 20	20	92	11·60 11·47	10·38 —	60·90 —
0·03	0·06	0·09	0·51	1 : 2 : 3 : 17	18	80	—	—	61·40
0·05	0·03	0·40	1	1 : 0·6 : 8 : 20	15	25	11·90	10·30	61·10
				Calculated for $Al_2TiCl_5C_6H_5$			11·67	10·35	61·30

(I) = referred to $TiCl_4$

($AlCl_3\cdot 2C_4H_8O$), it is possible to isolate a crystalline, green precipitate which proved to be a tetrahydrofuranate of titanium trichloride having the formula $TiCl_3\cdot 3C_4H_8O$.[11] By treatment of a toluene solution of $[AlTiCl_5C_6H_5]\cdot AlCl_3$ at −60° with tetrahydrofurane, a microcrystalline precipitate is obtained, dark-red in colour, insoluble in aromatic and aliphatic hydrocarbons.

When operating with a deficiency of the electron donor reactant in respect to the amount of $AlCl_3$ the precipitate corresponds to the formula $TiAlCl_5C_6H_5$.[11]

Analytical results and chemical behaviour of these complexes agree with both the structural formulae:



Formula (a) appears to be much more probable, at least in the normal state, than (b) as the bridges are symmetrical in respect to the axis passing through the titanium and aluminium atoms.

In formula (a) titanium is bound to aluminium by means of chlorine bridges, similar to those already found in the crystallizable complexes having general formula $(C_5H_5)_2TiCl_2AlR_1R_2$.

II. *Nature of Complexes Containing Titanium and Aluminium*

Titanium generally presents a lower tendency to form complexes in comparison with the heavier transition metals belonging to the same period. Therefore it may be of interest to discuss the nature of the complexes prepared by us. Most correspond to lower degree of oxidation than the maximum; some of which are rather unusual for titanium. Certain titanium complexes, containing only one metal atom having a degree of oxidation 4, were already known, but the chief interest, from the viewpoint of catalysis, is shown by the complexes containing more than one metal atom in their molecule. A degree of oxidation 4 is found in the compound $(C_5H_5)_2TiCl_2$ which, by itself, does not behave as a catalyst acting with an anionic co-ordinated mechanism. Assuming that titanium having a degree of oxidation 4 receives six electrons from each cyclopentadienyl group and two electrons from each chlorine ion, the number of electrons given by the ligand groups is 16 and the total number of electrons is 34. The number of electrons of krypton is therefore approached, without being reached. A similar electronic configuration should be presented by the complex $(C_5H_5)_2Ti(C_6H_5)_2$ as the bonds between phenyl groups and titanium are of the σ type, in contrast with the cyclopentadienyl groups which are bound to titanium by means of σ–π bonds.

When the degree of oxidation of titanium decreases, a tendency appears to form complexes containing more than one metal atom. $TiCl_3$ and $TiCl_2$ as distinct from $TiCl_4$ (which is a liquid, non-ionic compound), have high melting points. Their known crystalline modifications are all characterized by a co-ordination number 6. They exhibit an ionic nature, greater than $TiCl_4$, though the large force fields due to the presence of ions of a strong electro-positive metal, having a low valence and small diameter, do cause a close co-ordination of chlorine ions and their compact packing (mostly hexagonal compact). Owing to the large diameter of chlorine atoms, such a packing exhibits voids in which titanium atoms can find place (in the different modifications of $TiCl_3$ and in $TiCl_2$).[12]

Only the titanium atoms on the edge of each layer formed by packing of one plane of Ti atoms between two planes of Cl atoms, are not completely co-ordinated and can bind themselves with other groups. This may explain an epytactic adsorption of aluminium alkyls or chloroalkyls, by which the electro-negative groups complete the co-ordination of peripheral titanium atoms, while the aluminium atoms (having a small diameter) can epytactically occupy the positions of the metal corresponding to a peripheral growth of the lattice of $TiCl_3$.[1]

Titanium complexes having a degree of co-ordination 6 are more stable in the solid state owing to the force fields of the crystal. Crystalline complexes stable even in solution, having a degree of co-ordination 8, are those corresponding to the general formula $(C_5H_5)_2TiCl_2AlR_1R_2$.

As already pointed out, the X-ray examination revealed the presence of bridge bonds between Ti and Al, a tetrahedral pattern for the four groups co-ordinated to Al and also a slightly distorted tetrahedral configuration of the two cyclopentadienyl groups together with the two chlorine atoms in relation to titanium. The 3-centre bridge bonds allow aluminium to assume an sp^3, and titanium a d^4sp^3 hybridization. Trivalent titanium possesses only one (unpaired) electron on *d*-orbitals, and this is the reason for paramagnetic properties shown by complexes of this type.

[12] G. Natta, P. Corradini, I. W. Bassi and L. Porri, *Rend. Accad. Naz. Lincei* **24**, (8), 121 (1958).

The red complex $[CpTiCpAlR_2]_2$ appears to be of rather unusual structure. This is the very first case of a titanium complex corresponding to a degree of oxidation 1. The X-ray examination demonstrates the existence of two types of cyclopentadienyl groups: two of them, belonging to one type, are bonded by σ–π bonds to the Ti atoms, while the two others are linked to Al by means of σ–σ bonds (Fig. 2).

The position of the latter two cyclopentadienyl groups suggests that they may be bridge-linked both to titanium and to aluminium and furthermore are bonded by π bonds to titanium. The complex is diamagnetic owing to a probable Ti–Ti bond, confirmed by the small distance (3·1 Å) between the two Ti atoms. Furthermore, one can suppose that each Ti atom gives an electron pair to an Al atom, thus forming a bond of dative type.

A deeper X-ray study is being undertaken in our Institute; this study will better elucidate the structure of this complex, which also appears to be electron deficient.

III. *Catalytic Properties of Crystallizable Complexes Containing Titanium and Aluminium*

Table 3 shows that benzene solutions of the three complexes corresponding to the general formula $(C_5H_5)_2TiCl_2AlR_1R_2$ are able to promote, by themselves, ethylene polymerization yielding polymers of high molecular weight. However, the complex containing no alkyl groups exhibits an extremely low activity.

TABLE 3. CATALYTIC ACTIVITY OF COMPLEXES OF THE GENERAL FORMULA $(C_5H_5)_2TiCl_2AlR_1R_2$ (R_1 AND R_2 BEING —Cl OR $—C_2H_5$) IN THE POLYMERIZATION OF ETHYLENE AT 95° AND 40 ATM

Catalyst		Solvent		Time (hr)	Crystalline polyethylene (g)	Terminal groups found in the polymer
Type	moles	Type	cm^3			
$(C_5H_5)_2TiCl_2Al(C_2H_5)_2$	0·003	*n*-heptane	40	8	7	$—C_6H_5$
$(C_5H_5)_2TiCl_2AlC_2H_5Cl$	0·0035	*n*-heptane	40	8	8	$—C_6H_5$
$(C_5H_5)_2TiCl_2AlCl_2$	0·0046	toluene	50	21	3	$—C_5H_5$

In the case of complexes containing ethyl groups, it has been found, using C^{14} labelled alkyls, that each polymeric chain contains one of the ethyl groups initially present in the complex. On the other hand, in the case of the complex containing 4 chlorine atoms per molecule, we were able to establish, using C^{14} labelled cyclopentadienyl groups, the presence of these groups linked to the polymeric chains.[13] Ethylene polymerization by means of these complexes might, therefore, take place according to a mechanism similar to the one observed with catalysts acting by means of an anionic co-ordinated mechanism, by insertion of the monomeric molecules on a metal-organic bond which can be of the Al–C type or even of the Ti–C type.

However as far as it is known we cannot exclude that the polymerization of ethylene, by means of the above complexes, takes place only after the complex has been transformed into an activated form in which one bridge chlorine atom has

[13] G. Natta, G. Mazzanti, U. Giannini, G. Pajaro and S. Cesca, In press.

been substituted by an alkyl group or by a cyclopentadienyl group. In this way the relatively low activity shown by these complexes could be explained.

The possibility that the chain growth in anionic co-ordinated polymerization takes place through insertion of a polarized monomeric molecule on a bridge of an electron deficient molecule containing alkyl bridge bonds, had been already considered by Natta.*

Later, a mechanism of this type was proposed also by other authors.[14] The lower activity of the complex not containing alkyl groups could be explained by the much

TABLE 4. CATALYTIC ACTIVITY OF COMPLEXES OF THE GENERAL FORMULA $(C_5H_5)_2TiCl_2AlR_1R_2$ (WHERE R_1 AND R_2 ARE —Cl OR —C_2H_5) IN THE POLYMERIZATION OF ISOBUTYL-VINYL-ETHER, IN TOLUENE SOLUTION, AT −78°

Catalyst	Monomer/catalyst molar ratio	Time (hr)	Conversion of the monomer (%)	[η]	Properties of the polymer
$(C_5H_5)_2TiCl_2AlCl_2$	400	2	97	2·03	91 % insoluble in acetone; highly crystalline at X-rays.
$(C_5H_5)TiCl_2AlC_2H_5Cl$	300	3	34	2·15	55 % insoluble in acetone; highly crystalline at X-rays.
$(C_5H_5)_2TiCl_2Al(C_2H_5)_2$	35	10	0	—	—

[η] = intrinsic viscosity in toluene at 30°

higher energy of activation required for a bridge-like arrangement of the cyclopentadienyl nucleus (linked by π–σ bonds to titanium, in the non-activated state) between titanium and aluminium.

The hypothesis that catalytic activity is connected with an activated form of this type could explain the lack of catalytic activity of other titanium *bis*(cyclopentadienyl) compounds which are not able to form bridges in the molecule, such as *bis*(cyclopentadienyl) titanium dichloride, *bis*(cyclopentadienyl) titanium diphenyl or dimethyl, which do not alone promote ethylene polymerization.

By decreasing the number of alkyl groups in the complexes having the general formula $(C_5H_5)_2TiCl_2AlR_1R_2$, a cationic activity arises in these compounds, which enables them to promote, e.g. stereospecific polymerization of vinyl ethers (Table 4)[15]. In this case, contrary to what happens in ethylene polymerization, neither alkyl nor cyclopentadienyl groups initially bound to the catalytic complex, can be found in the polymer.

The complex $(C_5H_5)_2TiCl_2AlClC_2H_5$ is an interesting example of a catalyst able to promote stereospecific polymerisation through two different mechanisms, either cationic or anionic, depending on the ability of the monomers to polymerize by one or by the other mechanism.

The complex free of halogen atoms $[(C_5H_5)_2TiAl(C_2H_5)_2]_2$ can promote the polymerization of ethylene.[10]

As shown in Table 5, the polyethylenes contain high molecular weight fractions which, by X-ray examination prove to be highly crystalline and also low molecular weight fractions according to a wide dispersion in molecular weights.

* Opening Lecture of the Congress of Pure and Applied Chemistry, Paris, July (1957);[3] and Lecture given in Rome at the Symposium on the Chemistry of Co-ordination Compounds.[1]

[14] F. Patat and H. Sinn, *Angew. Chem.* **70**, 496 (1958).
[15] G. Natta, G. Dall'Asta, G. Mazzanti, U. Giannini and S. Cesca, *Angew. Chem.* **71**, 205 (1959).

TABLE 5. CATALYTIC ACTIVITY OF THE COMPLEX $[(C_2H_5)_3TiAl(C_2H_5)_2]_2$ IN THE POLYMERIZATION OF ETHYLENE, IN THE PRESENCE AND IN THE ABSENCE OF $TiCl_3$, USING TOLUENE AS SOLVENT OF THE MONOMER

Organometallic compounds		$TiCl_3$ moles . 10^3	Polymerization conditions			Poly-ethylene (g)	Fractionation of the polymer					
							Ether extractable fraction (%)	Boiling heptane extractable fraction		Residue		
Type	moles . 10^3		Temperature (°C)	Pressure (atm)	Time (hr)			(%)	$[\eta]$	(%)	$[\eta]$	Crystallinity (%)
$[(C_2H_5)_3TiAl(C_2H_5)_2]_2$	2·8	0	90	10	19	6·25	55	14·5	0·11	30·5	1·87	86
$[(C_2H_5)_3TiAl(C_2H_5)_2]_2$	2·2	0	90	40	8	11·3	13·3	13·9	0·12	72·8	2·75	85
$[(C_2H_5)_3TiAl(C_2H_5)_2]_2$	3·4	1·95	80	3	5	67·2	0·3	0·8	—	98·9	8·90	81
$Al(C_2H_5)_3$	6·5	2·08	80	3	5	82	0	1·4	—	98·6	8·45	84

$[\eta]$ = intrinsic viscosity in tetraline at 135°

The $[(C_5H_5)_2TiAl(C_2H_5)_2]_2$–$\alpha TiCl_3$ catalytic system polymerizes ethylene, yielding polymers having very high molecular weight and crystallinity (Table 5).

The same catalytic system promotes propylene polymerization at rates comparable with those obtained with the typical catalysts $Al(C_2H_5)_3$–$\alpha TiCl_3$, yielding polymers remarkably richer in isotactic macromolecules (not extractable by boiling n-heptane) (Table 6). These isotactic fractions possess higher molecular weights.[10]

The higher stereospecificity and higher degree of polymerization can be ascribed to the fact that chain transfers between the growing polymeric chains and the alkyl

TABLE 6. PROPYLENE POLYMERIZATION IN THE PRESENCE OF THE CATALYTIC SYSTEMS $TiCl_3$–$[(C_5H_5)_2TiAl(C_2H_5)_2]_2$ AND $TiCl_3$–$Al(C_2H_5)_3$—POLYMERIZATION CONDITIONS: TEMPERATURE 75°C; PROPYLENE CONSTANT PRESSURE 5 ATM; TIME 7 HOURS

Catalyst			Solvent		Poly-propylene (g)	Average rate of polymerization $\frac{g\ C_3H_6}{g\ TiCl_3 \cdot h}$	Isotactic polymers not extractable with boiling heptane	
Organometallic compounds		$TiCl_3$ moles $\cdot 10^3$	Type	cm^3			(%)	$[\eta]$
Type	moles $\cdot 10^3$							
$[(C_5H_5)_2TiAl(C_2H_5)_2]_2$	4·15	3·7	toluene	250	20·9	5·7	94·5	3·96
$Al(C_2H_5)_3$	9·0	4·1	toluene	250	68·6	15·5	83·1	2·58
$[(C_5H_5)_2TiAl(C_2H_5)_2]_2$	2·45	2·6	n-heptane	300	45·6	16·2	93·0	6·99
$Al(C_2H_5)_3$	8·4	4·2	n-heptane	500	97	21·3	85·2	4·17

$[\eta]$ = intrinsic viscosity in tetraline at 135°C

groups present in solution in the catalytic system, occur to a more limited extent in comparison with polymerization by means of the $Al(C_2H_5)_3$–$TiCl_3$ catalytic system. In fact, this reduced alkyl-transfer should be accompanied by a lower probability of inversion in steric configuration of the monomeric units entering the growing chain.[16]

TABLE 7. CATALYTIC ACTIVITY OF THE COMPLEX $[AlTiCl_5C_6H_5]\cdot AlCl_3$ IN THE POLYMERIZATION OF ETHYLENE—POLYMERIZATION CONDITIONS: TEMPERATURE 80°, INITIAL PRESSURE 25 ATM, TIME: 14 HOURS

$[AlTiCl_5C_6H_5]\cdot AlCl_3$ moles	Solvent		Polyethylene (g)	Fractionation of the polymer					
				Waxy polymers extractable with boiling acetone (%)	Boiling heptane extractable fraction		Residue		
	Type	cm^3			(%)	$[\eta]$	(%)	$[\eta]$	Crystal-linity (%)
0·007	benzene	100	12·6	28·0	6·4	0·14	65·0	1·28	85
0·003	heptane	100	15·5	26·1	23·4	0·15	49·4	0·90	86

$[\eta]$ = intrinsic viscosity in tetraline at 135°C

The complex having the formula $(AlTiCl_5C_6H_5)\cdot AlCl_3$, dissolved in benzene or suspended in heptane, promotes ethylene polymerization yielding waxy, low molecular weight polymers together with solid polymers containing high molecular weight fractions, crystalline under X-ray examination[11] (Table 7).

In the I.R. spectra of the polyethylenes thus obtained, an absorption band at 14·33 μ, attributable to phenyl groups bound to the polymeric chains, is easily detectable. Although the formation of linear polyethylenes, in which at least a part of the chains contains, as terminal groups, the phenyl group initially bound in the

[16] G. Natta, *Rend. Accad. Naz. Lincei* **24**, (8), 246 (1958).

complex, is to be ascribed to a polymerization mechanism of anionic type, the complex $(AlTiCl_5C_6H_5)\cdot AlCl_3$ exhibits also an acidic character. It can promote fast polymerization of propylene, yielding oily polymers, similar to the products of the polymerization of this monomer by means of $AlCl_3$ or $TiCl_4$. In this low molecular weight polypropylenes no phenyl group can be detected by I.R. analysis.

The solid, microcrystalline complex $AlTiCl_5C_6H_5$ promotes ethylene polymerization at a rate much higher than that observed with the complex $(AlTiCl_5C_6H_5)\cdot AlCl_3$, yielding polymers which are free of oily, low molecular weight fractions (Table 8).

In the I.R. spectra of fractions having the lower molecular weights (extractable by heptane), it was possible to detect the presence of phenyl groups bound to the polymeric chains.

This complex promotes the polymerization of propylene[11] (Table 8) but with an activity much lower than that of the most typical stereospecific catalysts[6] yielding linear polymers containing fractions made up of atactic macromolecules, stereoblock[17] fractions and fractions consisting of isotactic macromolecules.[4]

In the I.R. spectra of fractions having lower molecular weights (extractable by ether or by n-heptane) the presence of bands at 13, 16 and 14·33 μ was detected, attributable to benzylidene groups.

The initiation growth of the first polypropylene chains in the presence of complex $TiAlCl_5C_6H_5$ could therefore occur by addition of a monomeric molecule according to a reaction of the following type:

$$(TiAlCl_5)^{(+)(-)}C_6H_5 + CH_2{=}CH{-}CH_3 \rightarrow (TiAlCl_5)^{(+)(-)}CH_2{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}C_6H_5$$

Transfer reactions with the monomer[18] may successively originate other polymeric chains, according to an anionic mechanism, as proposed by us for other catalysts acting in the stereospecific polymerization of propylene.[19]

IV. *Nature of Anionic, Co-ordinated Polymerization*

Already in previous papers we had exposed our points of view on the nature of anionic co-ordinated catalysis.

We shall limit ourselves to point out here the contribution brought by the study of the catalytic properties of the new metallorganic complexes of definite composition.

All catalytically active complexes contain in their molecule two metal atoms. When comparing these results with those obtained using the most typical catalysts of the Ziegler type, for which complexes of defined composition have not so far been isolated in a pure crystallizable form, it can be assumed that, also for these catalysts, the active components are formed by electron deficient metallorganic complexes, containing in their molecules at least two metal atoms.

Whereas ethylene polymerization can take place also with catalysts soluble in the polymerization medium, anionic co-ordinated polymeri ation of alpha-olefines takes place only with catalysts acting in the presence of a heterogeneous solid phase. In

[17] G. Natta, G. Mazzanti, G. Crespi and G. Moraglio, *Chim. e Industr.* **39**, 275 (1957).
[18] G. Natta, I. Pasquon, E. Giachetti and F. Scalari, *Chim. e Industr.* **40**, 103 (1958).
[19] G. Natta, P. Pino, E. Mantica, F. Danusso, G. Mazzanti and M. Peraldo, *Chim. e Industr.* **38**, 124 (1956.)

TABLE 8. CATALYTIC ACTIVITY OF THE COMPLEX $AlTiCl_3C_6H_5$ IN THE POLYMERIZATION OF ETHYLENE AND OF PROPYLENE

$AlTiCl_3C_6H_5$ moles	Monomer	Polymerization conditions			Polymer (g)	Fractionation of the polymer							
		Temperature (°C)	Pressure (atm)	Time (hr)		Ether extractable fraction (%)	Boiling heptane extractable fraction			Residue			
							(%)	[η]	Crystallinity (%)	(%)	[η]	Crystallinity (%)
0·007	ethylene	85	20	3	114	0·25	1·1	0·11	80	98·65	9·0	87
0·004	propylene	110	25	16	24	80·3	10·85	0·89	45	10·15[a]	3·90	72

[a] In the case of polypropylene the residue after heptane extraction consists of isotactic macromolecules.

order that this polymerization results stereospecific, it is necessary that in the catalysts a crystalline structure or molecular aggregate having an ordered structure is present.

In catalysts containing titanium and aluminium, the same types of bridge bonds between the two metals are present, being the Ti atom either part of a soluble complex or present on the surface of a crystalline lattice.

In the latter case the initially incomplete co-ordination of titanium in certain peripheral regions of the lattice facilitates chemisorption of metal–organic compounds of strongly electropositive metals, having a small ionic radius (Al, Be, Mg).

Some authors,[20] stated that in polymerizations occurring in the presence of typical Ti–Al catalytic systems, the polymeric chains grow on titanium. According to these authors[20] we could not have foreseen this possibility and our statement referring to the growth of the polymeric chains on aluminium should be considered as incorrect. The possibility of existence of catalytic systems containing only titanium compounds had been previously demonstrated by us in preparing catalysts for the polymerization of ethylene and propylene by reacting *bis*(cyclopentadienyl) titanium diphenyl with $TiCl_4$. It can be assumed that, by means of this reaction, complexes containing at least two Ti atoms are formed.[21] In such cases the polymeric chain grows on a titanium atom (probably on the one which is more electropositive), or on a bridge between two Ti atoms. These catalysts have poor activity. A low activity is shown also by the catalysts obtained from methyl-titanium trichloride.[22] In order to have catalysts showing a high activity, the presence of another metal in the complex seems to be necessary.

The hypothesis that also in the case of catalysts prepared from titanium halides and Al-trialkyls the polymeric chain grows on a titanium–alkyl bond, disagrees with the following experimental results:

(1) The presence of phenyl groups, bound to the polymeric chains, has been ascertained in the case of ethylene polymerization by catalysts prepared from Al-triphenyl and $(C_5H_5)TiCl_2$. Terminal phenyl groups are not present in polyethylenes prepared with catalysts obtained from $(C_5H_5)_2Ti(C_6H_5)_2$ and Al-triethyl.[23]

(2) Investigations adsorbing $Al(C_2H_5)_3$ containing ^{14}C labelled alkyls on $TiCl_3$ and then polymerizing in the presence of non-labelled $Al(C_2H_5)_3$ proved that practically all the alkyl groups bound to aluminium previously adsorbed on α-$TiCl_3$ are found as terminal groups in polymeric chains. On the other hand it cannot be considered that all these alkyl groups were initially engaged in titanium alkylation.[24] Furthermore, at the polymerization end the major part of all the polymeric chains produced remain chemically bound to aluminium[25] as indicated by the chemical analysis of the polymerization products. This is probably due to a dissociation of each catalytic complex, in two parts, one containing the titanium atom, the other one containing alkyl groups (including polymeric chains) bound to aluminium. This dissociation is followed by an association involving other aluminium alkyls from the solution.

As previously mentioned, when dealing with the activity of complexes having

[20] D. B. Ludlum, A. W. Anderson and C. E. Ashby, *J. Amer. Chem. Soc.* **80**, 1380 (1958); E. J. Badin, *Ibid.* **80**, 6545 (1958); D. S. Breslow and N. R. Newburg, *J. Amer. Chem. Soc.* **81**, 81 (1959).
[21] G. Natta, P. Pino, G. Mazzanti and R. Lanzo, *Chim. e Industr.* **39**, 1032 (1957).
[22] Belg. Pat. 553, 477.
[23] G. Natta, P. Pino, G. Mazzanti, U. Giannini, E. Mantica and M. Peraldo, *J. Polymer Sci.* **26**, 120 (1957).
[24] G. Natta, G. Pajaro, I. Pasquon and V. Stellacci, *Rend. Accad. Naz. Lincei* **24**, (8), 479 (1958).
[25] G. Natta, L. Giuffre' and I. Pasquon, *Rend. Accad. Naz. Lincei* **25**, (8), 417 (1958).

general formula $(C_5H_5)_2TiCl_2AlR_1R_2$, we cannot exclude that in the case of Ti–Al catalytic systems the polymerization occurs by insertion of the monomeric molecules into a bridge in which alkyl groups link Ti to Al by means of 3-centre bonds.

In such a case it is difficult to distinguish whether the chain grows on Ti or on Al.

It may be assumed that the partial ionic dissociation of a complex

takes place as indicated in Fig. 3.

A first step of association of the monomer with the transition metal, caused by the high electronic density of the double bond and by the electron deficiency of the

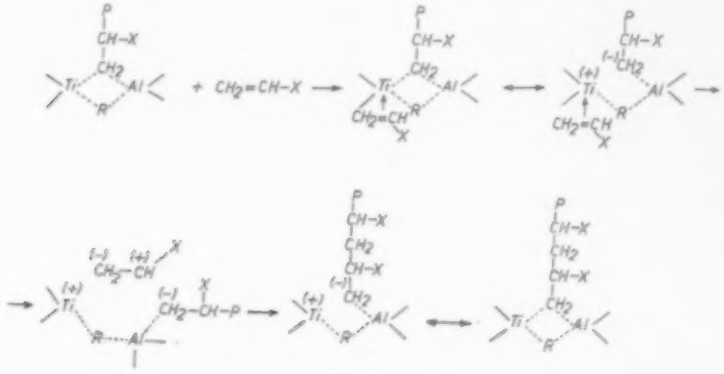


FIG. 3.

transition metal, is admissible. Kinetic data with α-$TiCl_3$–$Al(C_2H_5)_3$ catalytic systems agree with this hypothesis. In this way an explanation is available for the fact that the rate of certain transfer processes and the rate of growing process are both of the same order in respect to the monomer concentration,[26] as they were two parallel reactions following the same intermediate state. This step should be followed by a polarization of the double bond, of the entering monomeric unit as indicated in Fig. 3.

The chain growth must be ascribed to the neutralisation of the charge on the CHR group, belonging to the new monomeric unit, with the terminal CH_2 group of the polymeric chain, whilst it can be foreseen that the CH_2 group of the new monomeric unit links itself to the more electropositive metal, which is aluminium.

V. *Stereospecificity in Ionic Co-ordinated Polymerizations*

Many authors have interpreted our statement that stereospecific polymerization of alpha-olefines takes place only on catalysts acting in heterogeneous phase, should be extended also to the polymerization of other monomers.

It must be considered that our School was the first to obtain isotactic and syndiotactic polymers from diolefines and that these sterically regular polymers were prepared by means of soluble catalysts.[27] Furthermore, we have extended the

[26] G. Natta, I. Pasquon and E. Giachetti, *Makrom. Chem.* **24**, 258 (1957).
[27] G. Natta, L. Porri and G. Zanini, *Chim. e Industr.* In press.

stereospecific polymerizations of vinyl ethers to some soluble catalysts[15] different from those proposed by Schildknecht.[28]

When the monomer contains two groups rich in electrons (two double bonds in diolefines or one double bond and one oxygen with a lone electron pair in the case of vinyl ethers) an association of the monomeric molecules with the electron deficient catalyst should be possible before the addition to the growing polymeric chains, even if the catalyst does not contain a heterogeneous phase, able to adsorb the monomer. In such cases a stereospecific polymerization can take place through soluble catalytic complexes.

In fact, soluble catalysts are the reaction product between chromium-acetylacetonate and Al-trialkyls used by us for the synthesis of isotactic and syndiotactic polymers of diolefines.[27]

Also soluble are the compounds having a weak cationic activity and able to form etherates [$(AlClR_2)_2$; $(AlCl_2R)_2$; $TiCl_2(OR)_2$] used by us for the cationic stereospecific polymerization of alkyl-vinyl-ethers.[15] Therefore, excluding the case of the polymerizations of α-olefines, stereospecific polymerizations are not necessarily connected with the presence of insoluble catalysts acting from the beginning of the polymerization in hererogeneous phase.

[28] C. E. Schildknecht, A. O. Zoss and C. McKinley, *Industr. Engng. Chem.* **39**, 180 (1947); C. E. Schildknecht, S. T. Gross, H. R. Davidson, J. M. Lambert and A. O. Zoss, *Ibid.* **40**, 2104 (1948); C. E. Schildknecht, A. O. Zoss, G. Grasser, *Ibid.* **41**, 2891 (1949).

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SOLVENT EFFECTS IN THE REACTIONS OF FREE RADICALS AND ATOMS—VI

SEPARATION OF POLAR AND RESONANCE EFFECTS IN THE REACTIONS OF CHLORINE ATOMS[1]

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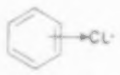
(*Received* 16 *July* 1959)

Abstract—Aromatic solvents have a large effect upon the reactivity of chlorine atoms toward carbon–hydrogen bonds having different bond dissociation energies. When the difference in reactivity of two carbon–hydrogen bonds is determined by polar effects, aromatic solvents have little effect upon the relative reactivities toward chlorine atoms. Two polar effects are important in the reactions of atoms and radicals with carbon–hydrogen bonds. When extensive bond rupture in the transition state occurs, a resonance contribution to the transition state involving charge separation is important (e.g. bromine atoms). For an atom as reactive as chlorine where little bond breaking occurs in the transition state, the polar effect is best considered in terms of a repulsion curve between the chlorine atom and the carbon–hydrogen bonds, repulsion being higher the lower the electron density of the carbon–hydrogen bond.

LARGE solvent effects have been observed in the competitive photochlorination of primary, secondary and tertiary carbon–hydrogen bonds.[2] Aromatic solvents have an effect proportional to their basicity suggesting the formation of a complexed chlorine atom which is more selective and less reactive than a free chlorine atom.

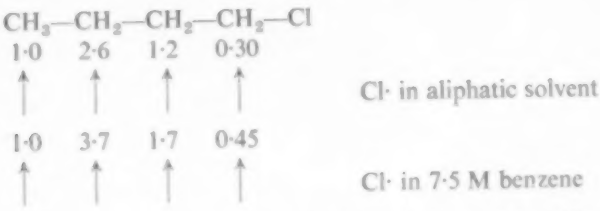


From a study of numerous chlorinations it was suggested that relative reactivities determined mainly by the availability of electrons in the carbon–hydrogen bonds (control by polar factors) are not particularly sensitive to solvent effects whereas relative reactivities determined mainly by the stabilities of the incipient free radicals (control by resonance factors) are very sensitive to changes in solvent. For example, the relative reactivities of the tertiary and primary hydrogen atoms of 2,3-dimethylbutane toward the chlorine atom at 25° increases from 4·2 : 1 in an aliphatic solvent to 20 : 1 in 4 M benzene to 225 : 1 in 12 M carbon disulfide.[2] Similarly, the relative reactivities of the secondary and primary hydrogens of n-pentane increase from 3·6 : 1 to 4·6 : 1 to 30 : 1. In both cases the strengths of the carbon–hydrogen bonds being ruptured are mainly responsible for the observed reactivities. On the other hand, when the relative reactivities of the hydrogen atoms of tetramethylsilane and trimethylchlorosilane are compared, the relative reactivity changes from 6·5 : 1 in an aliphatic solvent to 6·9 : 1 in 4 M t-butylbenzene to 5·1 in 12 M carbon disulfide. Although

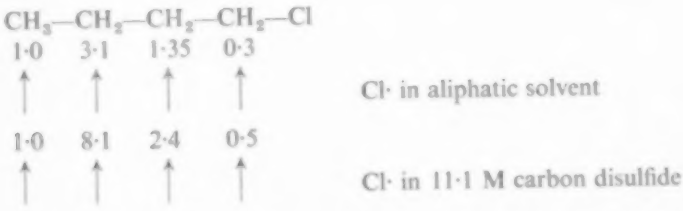
[1] Directive Effects in Aliphatic Substitutions—XIV.
[2] G. A. Russell, *J. Amer. Chem. Soc.* **79**, 2977 (1957); **80**, 4987, 4997, 5002 (1958).

tetramethylsilane is considerably more reactive toward a chlorine atom than is trimethylchlorosilane, presumably because of the polar effect of the chlorine substituent, only a small effect of solvent upon relative reactivity was observed.

The suggestion that the relative importance of polar effects and resonance effects in determining reactivity toward a chlorine atom could be separated by observations of the magnitude of the solvent effect has been discussed by Walling and Mayahi[3] and has been recently criticized by den Hertog and Smit.[4] However, at the present time the available data is in good agreement with the afore-mentioned suggestion. Estimates of the magnitudes of the solvent effects observed can be obtained from the data of Walling and Mayahi.[3] Thus, in the photochlorination of n-butyl chloride at 68° the following relative reactivities per hydrogen atom can be calculated.



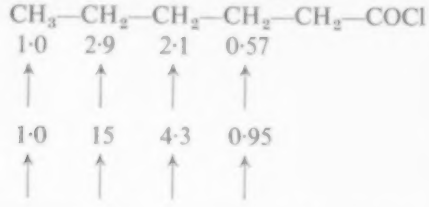
In the 3- and 4-positions relative reactivities are determined by differences in bond dissociation energies and an increase from 2·6 to 3·7 (an increase of 40 per cent) is noted between an aliphatic solvent and 7·5 M benzene. In the 3- and 2-positions the large difference in reactivity may be connected with the polar effect of the chlorine substituent. Here, however, the relative reactivities change only from 2·1 : 1 in an aliphatic solvent to 2·25 : 1 in 7·5 M benzene (a change of 7 per cent). Little effect of solvent is noted for the relative reactivities of the hydrogen atoms at the 1- and 2-positions. In the presence of carbon disulfide at 0° the following relative reactivities were observed.



Again a large solvent effect upon the relative reactivities of the 3- and 4-hydrogen atoms was noted (an increase of 160 per cent). When the 3- and 2-positions are compared relative reactivity changes from 2·3 : 1 to 3·3 : 1 (a change of 45 per cent) while the relative reactivities at the 1- and 2-positions change only by 10 per cent. These results are in complete accord with one original suggestion.[2] The relative reactivities at the 1-, 2-, and possibly 3-positions are determined mainly by the polar effect of the chlorine substituent. The solvent effect upon the relative reactivities of the 3- and 4-hydrogens is 4–20 times as great as the solvent effect upon the relative reactivities of the 1-, 2- and 3-hydrogen atoms.

[3] C. Walling and M. F. Mayahi, *J. Amer. Chem. Soc.* **81**, 1485 (1959).
[4] H. J. den Hertog and P. Smit, *Proc. Chem. Soc.* 132 (1959).

The recent results of den Hertog and Smit[4] suggest a similar interpretation. They report that the relative reactivities of the α- and β-hydrogens of propionyl chloride (1 : 2·5) are relatively independent of solvent.[4] Here the relative reactivities are determined mainly by the polar effect since the primary hydrogen atom is considerably more reactive than the secondary hydrogen atom. We might expect aromatic solvents to increase the proportion of attack of the α-position (i.e., at the weakest carbon-hydrogen bond) and indications are that this is indeed the case.[5] From their reported products of the chlorination of hexanoyl chloride at 20° the following reactivities per hydrogen atom can be calculated.



Comparing the primary and secondary hydrogen atoms at the ε- and δ-positions indicates a solvent effect of 400 per cent upon the selectivity when the solvent is changed from the acid chloride itself to approximately 6·5 M benzene. When the relative reactivities of the β- and γ-hydrogens are compared only a small solvent effect is noted. Relative reactivities (γ : β) vary from 3·6 : 1 in an aliphatic solvent to 4·5 : 1 in benzene (a change of 25 per cent). This is consistent with our suggestion since den Hertog and Smit point out that the relative reactivities at the ε- and δ-positions are determined mainly by bond dissociation energies while the relative reactivities of the β- and γ-positions are determined mainly by polar effects.

The high reactivity of the δ-position in the presence of benzene (relative to the ε- or γ-positions) is surprising, and in view of the experimental uncertainties involved in the analysis of isomeric alkyl chlorides by distillation techniques, may be in error. By analogy with n-pentane,[2] n-butane[3] and n-butyl chloride[3] we might have expected the presence of 6·5 M benzene to increase the reactivity of the δ-hydrogen to about 6–7 times that of the ε-hydrogen rather than the 15-fold factor reported. The conclusion of den Hertog and Smit that solvents can have a pronounced effect on relative reactivities determined by the polar effect is based solely on the reactivity of the δ-position of hexanoyl chloride, and as mentioned earlier, is not supported when the β- and γ-positions are compared even though the difference in reactivity resulting from the polar effect is greater between the β- and γ-positions than between the γ- and δ-positions.

Variations in bond dissociations energies for the carbon hydrogen bonds in the 2- and 3-positions of n-butyl chloride and the γ- and δ-positions in n-hexanoyl chloride may be completely responsible for the solvent effects observed in the chlorination of these compounds. Fredericks and Tedder have recently reported rather compelling evidence that radicals with the structure CH_3—CH—CH_2—are more stable than radicals with the structure —CH_2—CH—CH_2—, presumably because of hyperconjugative stabilization.[6] These workers were able to demonstrate that the chlorine atom of n-pentyl chloride has no deactivation effect upon hydrogen atoms in the 3-position.

[5] H. J. den Hertog, Private communication.
[6] P. J. Fredericks and J. M. Tedder, *Chem. & Ind.* 490 (1959).

However, because of the difference in bond dissociation energies the 4-position of n-pentyl chloride is 1·5 times as reactive as the 3-position toward a chlorine atom at 78° (vapor phase). Such behavior is consistent with the conclusion that in chlorination the relative reactivities of 2°- to 1°-hydrogen atoms decrease in the order propane > n-butane > n-pentane > n-hexane.[7]

Another factor that argues that solvent effects are not particularly important when the reactivities of the hydrogen atoms are determined by polar effects is that there is no consistency in the direction of the *small* effects observed. In the chlorination of

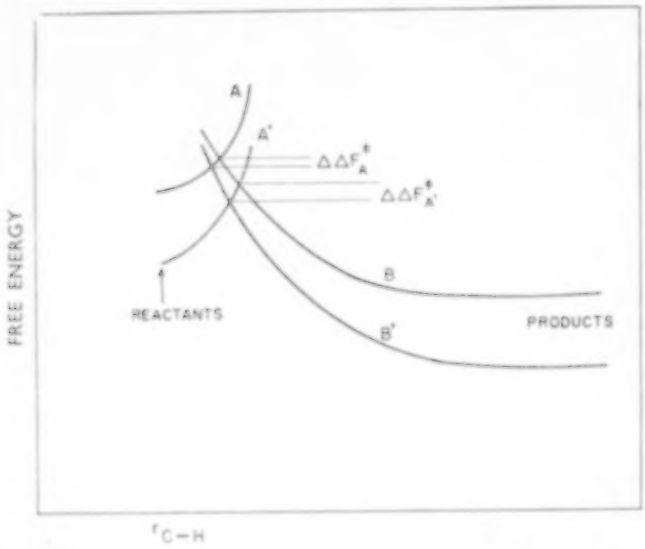


FIG. 1. Rationalization of solvent effect in reactions of chlorine atoms.

n-hexanoyl chloride in benzene solution[4] or n-butyl chloride in carbon disulfide solution[3] the solvents appear to accentuate the polar effect whereas in the chlorination of n-butyl chloride at 68°,[3] the competitive chlorination of tetramethylsilane and trimethylchlorosilane,[2] and the competitive chlorination of toluene and *p*-chlorotoluene,[5] aromatic solvents decrease the importance of polar effects.* It is uncertain whether any significance can be attached to these small effects which fit no consistent pattern, particularly in view of the fact that the carbon–hydrogen bond dissociation energies involved are not known accurately.

A rationalization of the effects of solvents upon the reactivity of carbon–hydrogen bonds can be made by use of energy diagrams. In Fig. 1 a possible diagram is given

* *Note added in proof*, 1 *December* 1959:—A careful reinvestigation by Mr. Roger C. Williamson of the competitive chlorination of toluene and *p*-chlorotoluene has failed to reveal the solvent effect previously reported by Walling and Miller.[5] We find at 40° that the relative reactivities of the benzyl hydrogenatoms of toluene and *p*-chlorotoluene toward chlorine atoms are 1·26 ± 0·03 : 1 in carbon tetrachloride solution. At a constant toluene to *p*-chlorotoluene ratio of 1 : 2 this relative reactivity is independent of the total concentration of aromatic hydrocarbons between 0·05 and 1 M and of the percent reaction between 5 and 35 mole % chlorination. Chlorination of a 1 M solution of a 1 : 2 mole ratio of toluene and *p*-chlorotoluene in benzene at 40° gives a relative reactivity of 1·29 : 1, a value indistinguishable from the result observed in carbon tetrachloride solution.

[7] G. C. Chambers and A. R. Ubbelohde, *J. Chem. Soc.* 285 (1955); E. T. McBee, H. B. Hass and J. A. Pianfelli, *Industr. Engng. Chem.* **33**, 185 (1941).

[5] C. Walling and B. Miller, *J. Amer. Chem. Soc.* **79**, 4181 (1957).

for the attack of free (A) and complexed (A′) chlorine atoms upon two carbon–hydrogen bonds (B and B′) of different strengths but of the same electron density. Curve A is a repulsion curve between the free chlorine atom and either of the hydrogen atoms.[9] Curve A′ is the repulsion curve for the complexed chlorine atom and is displaced from A by the energy of complex formation. Curves B and B′ describe the repulsion between alkyl radical and hydrogen chloride as well as the differences in radical stabilization of the two alkyl radicals. Since $\Delta\Delta F^{\ddagger}_{A'} > \Delta\Delta F^{\ddagger}_{A}$, the complexed chlorine atom will be considerably more selective than the free chlorine atom and large

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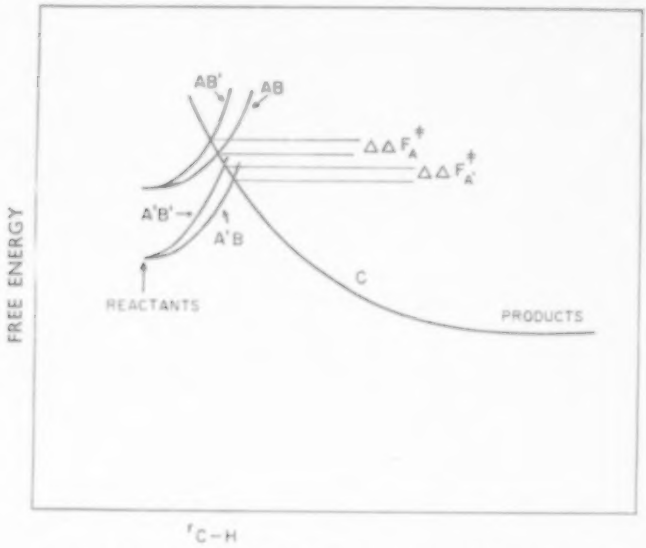

FIG. 2. Rationalization of polar effect in reactions of chlorine atoms.

solvent effects will be observed in the competitive chlorination of the two carbon–hydrogen bonds.

On the other hand, when a chlorine atom and a complexed chlorine atom attack carbon–hydrogen bonds of equal strength but different electron densities a different energy profile results. A possible situation is shown in Fig. 2. Curve AB′ is the repulsion curve for the attack of a free chloride atom on the carbon–hydrogen bond of lowest electron density and curve AB for attack on the bond of highest electron density. Curves A′B′ and A′B are the corresponding curves for the complexed chlorine atom. Curve C is again the repulsion curve between hydrogen chloride and either of the alkyl radicals. In this instance besides displacing the origin of A′B′ and A′B from the origin of AB′ and AB by the energy of complex formation, the curvature of A′B′ and A′B has been made greater than the curvature of AB′ and AB. This seems reasonable because complexing should decrease the electron deficiency of the

[9] Previous arguments [G. A. Russell and H. C. Brown, *J. Amer. Chem. Soc.* **77**, 4031 (1955)] have indicated that the transition state for the attack of a chlorine atom upon carbon–hydrogen bonds involves very little bond breaking since differences in stabilities of transition states reflect only about 10 per cent of the energy differences between the products.

chlorine atom[8] and increase the repulsion between the chlorine atom and the carbon–hydrogen bond (similarly in Fig. 1 A′ has been drawn with more curvature than A).[10] As drawn, $\Delta\Delta F^{\ddagger}_{A}$ and $\Delta\Delta F^{\ddagger}_{A'}$ are not particularly different, in agreement with the observed facts.

The polar effect described in Fig. 2 might be termed the inductive polar effect. It is capable of explaining all the polar effects observed in chlorination, including the surprising result that toward chlorine atoms a cyclohexane hydrogen atom is considerably more reactive than a toluene hydrogen atom.[11] Another polar effect recognized in the reaction of atoms and radicals involves contributions to the transition state of structure I.[12]

$$R^{+}\dot{H}\ :\ddot{\underset{\cdot\cdot}{X}}:^{-}$$

This resonance polar effect would be shown in a free energy diagram as a rounding off of the curve intersections. A resonance polar effect of this type fails to explain the relative reactivities of toluene and cyclohexane toward the chlorine atom but may be partially responsible for the fact that toward the bromine atom, where the transition state involves much more bond breaking and resonance stabilization, a toluene hydrogen atom is 250 times as reactive as a cyclohexane hydrogen at 80°.[11]

Further support for the consideration of two polar effects in the reactions of atoms and radicals with carbon–hydrogen bonds results from the observation that toward *m*- and *p*-substituted toluene derivatives relative reactivities toward the bromine atom are proportional to the σ^{+}-constant of the substitutent while toward the chlorine atom σ-constants fit the data somewhat better than σ^{+}-constants.[13] The stabilities of I would be expected to be proportional to σ^{+} while the electron densities of the benzyl–hydrogen bonds and therefore the shapes of the repulsion curves toward chlorine atoms would be determined by the σ-constant of the substituent.[14]

[10] The electron deficient chlorine atom is attracted by the electrons of the carbon–hydrogen bond. A reduction in the electron deficiency of the chlorine atom will decrease this attraction and increases the repulsion.

[11] G. A. Russell and H. C. Brown, *J. Amer. Chem. Soc.* **77**, 4578 (1955).

[12] F. R. Mayo and C. Walling, *Chem. Rev.* **46**, 191 (1950); G. A. Russell, *Tetrahedron* **5**, 101 (1959).

[13] G. A. Russell, *J. Org. Chem.* **23**, 1407 (1958).

[14] The relative rates of attack of bromine atoms, N-succinimdyl radicals [E. C. Kooyman, R. Van Helden and A. F. Bickel, *Koninkl. Ned. Akad. Wetenschap, Proc.* **56B**, 75 (1953)], peroxy radicals [G. A. Russell, *J. Amer. Chem. Soc.* **78**, 1047 (1956)] and trichloromethyl radicals [E. Huyser, *Ibid.* In press] upon benzylic hydrogen atoms are correlated by σ^{+} whereas the attack of the more reactive chlorine atoms[8] or t-butoxy radicals [C. Walling, *Abstracts of Papers presented at the 16th National Organic Chemistry Symposium, Seattle*, 1959, p. 85] are better correlated by σ.

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PRODUCTS OF NUCLEOPHILIC DISPLACEMENT REACTIONS IN THE ANTHRAQUINONE SERIES

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(*Received* 22 *June* 1959)

Abstract—Several unusual products are described, obtained from the reactions of 1-chloro-2-nitroanthraquinone, 2-bromo-3-nitroanthraquinone, etc with hydrazine, acylhydrazines, pyridine, 2-aminopyridine and toluenesulfonamide.

Although the displacement of either a halogen atom or a sulfo or nitro group from anthraquinone compounds by various reagents (particularly amines) is well known, relatively little has been reported concerning such reactions upon halonitroanthraquinones. The halogen atom of 1,5- or 1,8-chloronitroanthraquinones is displaced upon reaction[1] with *p*-toluenesulfonamide, as are, reportedly, those of 1,5-dichloro-4,8-dinitro- and 1,8-dichloro-4,5-dinitroanthraquinones upon treatment[2] with diethylamine, although in the latter two compounds the nitro groups also were displaced under more vigorous conditions, or upon reaction[3] with *p*-toluidine. Both the chlorine and the nitro group of 1-chloro-4-nitroanthraquinone were displaced[4] by *p*-toluidine, whereas only the chlorine was displaced by 1-amino-4-nitroanthraquinone.[5] Replacement of the chlorine atom was reported[6] in the reaction of 1-chloro-2-nitroanthraquinone with sodium acetate, diethylamine or 2-aminoanthraquinone, while aniline displaced the nitro group of 1-nitro-2-chloroanthraquinone.

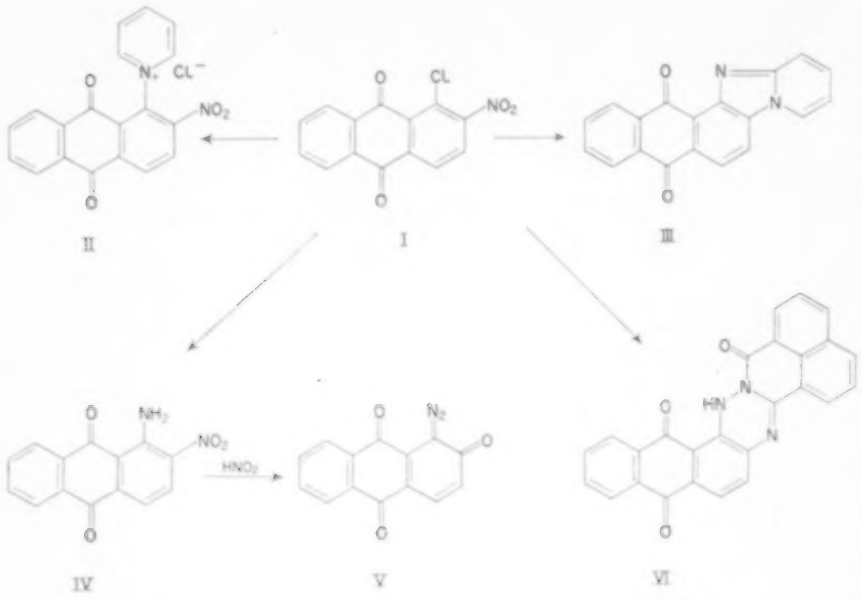
With halonitroanthraquinones now conveniently available[7] via the peracetic acid oxidation of aminohaloanthraquinones, we began a study of their reactions with nucleophilic reagents, particularly those capable of forming more complex products, and those leading to selective displacement.

A. Reactions of 1-*chloro*-2-*nitroanthraquinone*

When 1-chloro-2-nitroanthraquinone[7] (I) was heated in pyridine, the quaternary salt II was formed rapidly. While many halogen compounds react in this manner with pyridine, this reaction in the anthraquinone series is apparently novel. Even anthraquinones containing an "activated" halogen (e.g. 2-carbomethoxy-1-chloroanthraquinone or 1-chloro-2-cyanoanthraquinone) give no sign of reaction when heated briefly in pyridine. We therefore attempted the preparation of III, since it was known[8] that 2,4-dinitrochlorobenzene reacts readily with 2-aminopyridine to yield 3-nitropyrido[1,2-*a*]benzimidazole. In amyl alcohol, no reaction occurred

[1] F. Ullman and P. Kertész, *Ber. Dtsch. Chem. Ges.* **52**, 545 (1919).
[2] Bayer, *Ger. Pat.* 137,782; *Frdl.* **6**, 1304 (1904).
[3] Bayer, *Ger. Pat.* 127,458/9; *Frdl.* **6**, 363/4 (1904).
[4] Bayer, *Ger. Pat.* 126,803; *Frdl.* **6**, 362 (1904).
[5] Meister, Lucius and Brüning, *Ger. Pat.* 254,186; *Frdl.* **11**, 614 (1915).
[6] W. Bradley and E. Leete, *J. Chem. Soc.* 2129 (1951).
[7] W. L. Mosby and W. L. Berry, *Tetrahedron* **5**, 93 (1959).
[8] G. Morgan and J. Stewart, *J. Chem. Soc.* 1057 (1939).

between I and 2-aminopyridine, and in dichlorobenzene decomposition supervened. However, in glycol diacetate, a low yield of III was produced.



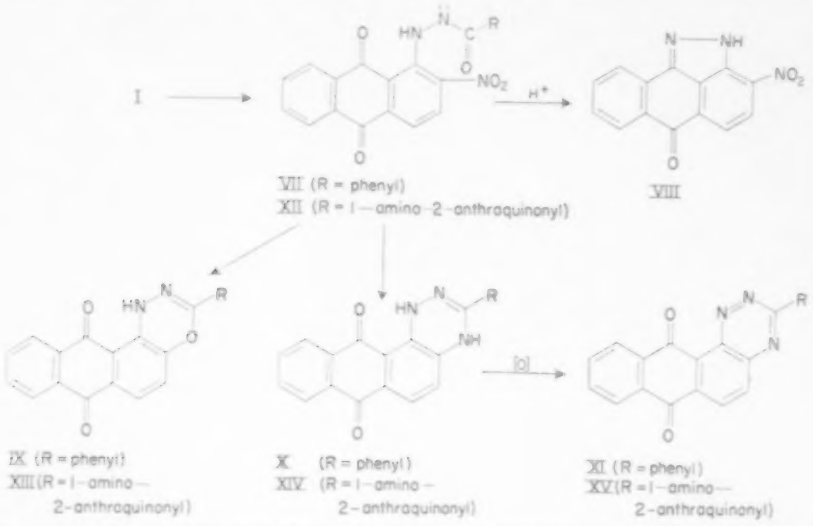
The reaction of I with *p*-toluenesulfonamide readily afforded the toluenesulfonamido intermediate from which the amine IV was obtained upon hydrolysis. Compound IV has been obtained, together with the 1,4-isomer, by the nitration of 1-aminoanthraquinone[9] or 1-anthraquinonylurethane,[10] and by the peracetic acid oxidation of 1,2-diaminoanthraquinone.[11] Treatment of IV with nitrous acid produced the diazo oxide V, which, because of its instability, could not be obtained analytically pure. However, the infrared spectrum of the compound and its ability to couple with H-acid indicate its structure.

When I was allowed to react with N-aminonaphthalimide,[12] N-(2-nitro-1-anthraquinonylamino)naphthalimide was formed. Reduction of the nitro group with sodium sulfide (or upon vatting) was accompanied by closure of the 1,2,4-triazine ring to yield the deep blue product VI.

The reaction of I with benzhydrazide afforded VII, which underwent acidic hydrolysis to yield VIII. Heating VII with potassium hydroxide in methyl Cellosolve produced two products: the oxadiazine IX, and 1-benzoylhydrazino-2-(2-methoxyethoxy)-anthraquinone formed by displacement of the nitro group by the solvent.

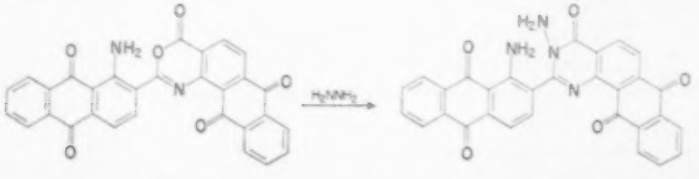
[9] Badische Anilin- und Sodafabrik, *Ger. Pat.* 279,866; *Frdl.* **12**, 419 (1917).
[10] Bayer & Co. *Ger. Pat.* 167,410; *Frdl.* **8**, 297 (1908).
[11] I. G. Farbenindustrie, A. G., *P.B. Report No.* 70341, frame 14040.
[12] Previously prepared by heating naphthalic anhydride with hydrazine in ethanol[13] or aqueous acetic acid.[14] These solvents offer disadvantages in preparing more than small amounts of material however, and we found aqueous pyridine[15] or, better still, dimethylformamide to give superior results. The use of glacial acetic acid as a solvent produced only N-acetamidonaphthalimide.
[13] A. Bistrzycki and J. Risi, *Helv. Chim. Acta* **8**, 810 (1925).
[14] A. Ostrogovich and M. Mihailescu, *Gazz. Chim. Ital.* **41**, II, 757 (1912); *Chem. Zentr.* I, 813 (1912).
[15] K. Wilke, *P.B. Report No.* 70339, frame 10986.

Treatment of VII with aqueous sodium sulfide gave the deep blue dihydrotriazine X, which was easily oxidized to XI. An analogous reaction sequence was completed from XII (obtained by reacting I with 1-amino-2-anthraquinone carbohydrazide[16]). Attempts to purify XII by recrystallization, produced compound XIII, and the latter accompanied XIV in the reduction of XII with sodium sulfide. Possibly catalytic hydrogenation would have given superior results, but this was not investigated.

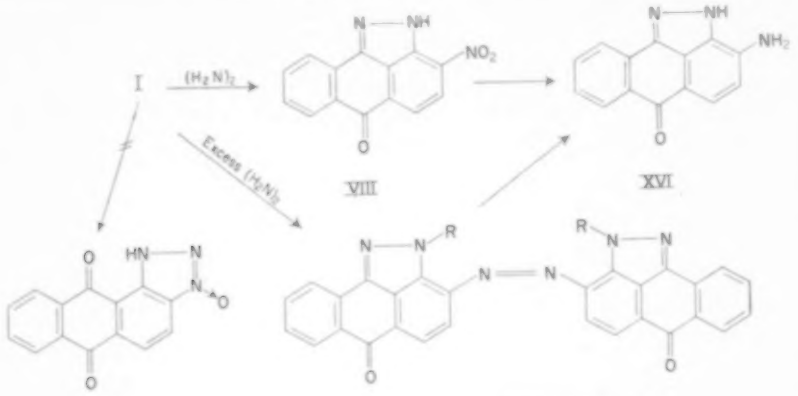


The conversion of VII and XII into X and XIV is similar to the method employed by Bischler[17,18] for the synthesis of benzo-1,2,4-triazine and its 3-methyl homolog. Despite its simplicity, the method does not appear to have been used since, with one exception. Raab[19] described the preparation of the 5-chloro homolog of X from the reaction of 2-benzamido-1,3-dichloranthraquinone with hydrazine. With this exception, anthra-[2,1-*e*][1,2,4]triazines and anthra[1,2-*e*][1,3,4]oxadiazines have not previously been described, although 2-(2-anthraquinonyl)-[1,2,4]triazines were prepared[20,21] recently.

[16] F. Ebel and R. Randebrock, *U.S. Pat.* 2,717,898.
[17] A. Bischler, *Ber. Dtsh. Chem. Ges.* **22,** 2801 (1889).
[18] A. Bischler and S. Brodsky, *Ber. Dtsch. Chem. Ges.* **22,** 2809 (1889).
[19] H. Raab, *P.B. Report No.* 70339, frame 11446.
[20] P. V. Laakso, R. Robinson and H. P. Vandrewala, *Tetrahedron* **1,** 103 (1957).
[21] In the preparation of the "anhydride" of 1-amino-anthraquinone-2-carboxylic acid[20] no structure was shown, although G. Stein [*P.B. Report No.* 70340, frame 12853] indicated the anhydride to have structure A. This suggests structure B for the product of "unknown identity" obtained[20] by treating A with hydrazine. This possibility is strengthened by recent work [N. S. Dokunikhin and I. D. Pletneva, *Zh. Obschei Khim.* **28,** 1019 (1958)] demonstrating the preparation of anthra[1,2-*d*]pyrimidones from anthra[1,2-*d*][1,3]oxazinones.



Next, the reactions of I with hydrazine were examined. Although 1-hydrazino-2-nitroanthraquinone undoubtedly is formed, only products of its further reaction were isolated. The addition of two molar equivalents of hydrazine to a solution of I in dimethylformamide afforded an excellent yield of 3-nitropyrazolanthrone (VIII). Reduction of VIII yielded XVI, which also was prepared from 2-benzamido-1-chloroanthraquinone. Structure XVII, initially considered along with VIII for the reaction product, seems unlikely in view of (1) similarities between the infrared spectrum of this product and those of other pyrazolanthrones, and (2) the reduction under mild conditions to XVI, unlikely to occur in the case of XVII. The reaction of I with less than two moles of hydrazine hydrate gave mixtures of I and VIII.



Treatment of I with an excess of hydrazine (ten moles) produced a different product. Microanalyses indicated the empirical formula $C_{14}H_7N_3O$, and alkaline reduction yielded XVI. The deep blue color of the vat solution of this substance recalled the colors of the vat solutions of the N,N′-dialkyl-3,3′-bispyrazolanthronyls,[22] and particularly of the N,N′-dimethyl-3,3′-vinylenebispyrazolanthronyls.[23] The product formed a copper chelate derivative when treated with cupric acetate in dimethylformamide. Accordingly, structure XVIII was assigned to the product Methylation of XVIII yielded XIX.

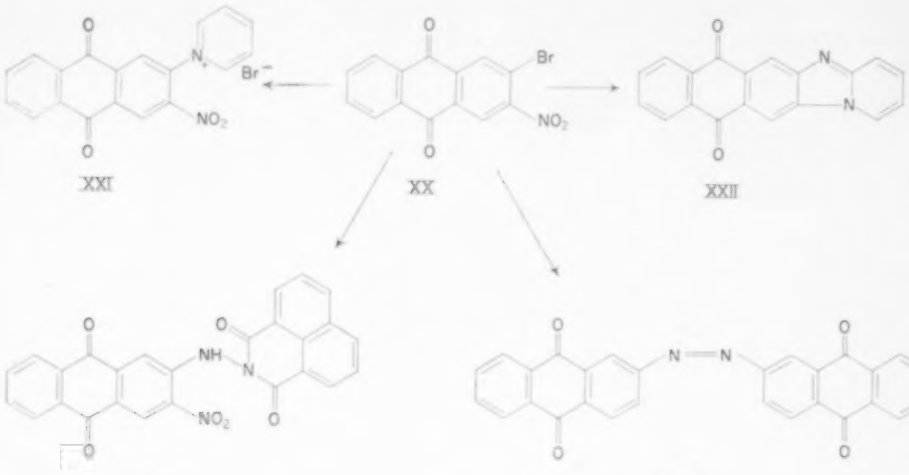
B. Reactions with 2-bromo-3-nitroanthraquinone

Heating 2-bromo-3-nitroanthraquinone[7] (XX) with pyridine readily afforded the pyridinium salt XXI, while with 2-aminopyridine, the linear quinone XXII resulted. The reaction of XX with *p*-toluenesulfonamide, followed by hydrolysis of the resulting toluenesulfonamido intermediate, yielded 2-amino-3-nitroanthraquinone. This compound has been obtained previously, together with other products, by the nitration of 2-amino-anthraquinone[24] or 2-anthraquinonylurethane.[25]

When XX was condensed with N-aminonaphthalimide, compound XXIII was obtained. However, reduction of this product (by vatting) did not produce the

[22] W. Bradley and K. W. Geddes, *J. Chem. Soc.* 1636 (1952).
[23] G. Kalischer and H. Scheyer, *Ger. Pat.* 517,845; *Frdl.* **17**, 1275 (1932).
[24] R. Scholl, G. Schneider and F. Eberle, *Ber. Dtsch. Chem. Ges.* **37**, 4427 (1904).
[25] F. Ullman and R. Medenwald, *Ber. Dtsch. Chem. Ges.* **46**, 1798 (1913).

linear analog of compound VI, but gave only 2,3-diaminoanthraquinone. The reasons for cleavage of the hydrazide in this instance, but not in the case of the angular isomer, are not apparent.



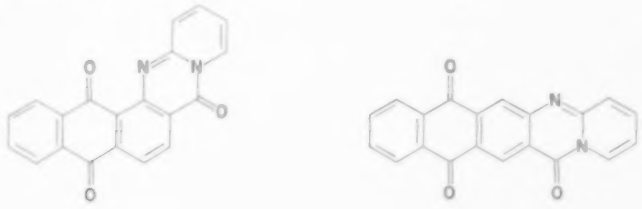
XXI XX XXII

XXIII XXIV

Another anomalous reaction appeared when XX was treated with hydrazine. The major product formed was 2-amino-3-bromoanthraquinone, but a halogen-free by-product also was isolated. Upon the bases of microanalyses and infrared spectrum, structure XXIV was assigned tentatively to this substance.

C. Miscellaneous

Reaction of 2-chloro-1-nitroanthraquinone[7] with benzhydrazide occurred slowly, and always yielded mixtures of the chloronitroanthraquinone with N′-(2-chloro-anthraquinonyl)-benzhydrazide. Treatment of the latter substance with sulfuric acid afforded 3-chloropyrazolanthrone.



XXV XXVI

In the course of these studies, a number of other displacement reactions were run. Three of these, although not involving halonitroanthraquinones, may be reported here. The reaction of 2-carbomethoxy-1-chloroanthraquinone[26] with 2-aminopyridine yielded a product assigned structure XXV, insomuch as the condensation of 2-chlorobenzoic acid with 2-aminopyridine has been reported[27,28] to

[26] F. Ullmann and H. Bincer, *Ber. Dtsch. Chem. Ges.* **49**, 732 (1916).
[27] O. A. Seide, *Liebigs Ann.* **440**, 311 (1924).
[28] O. A. Seide and G. W. Tschelinzew, *J. Gen. Chem. U.S.S.R.* **7**, 2314 (1937); *Chem. Zentr.* I, 601 (1938).

yield 11*H*-pyrido[1,2-*b*]quinazol-11-one. An attempt to prepare XXVI by an analogous reaction with 2-carbomethoxy-3-chloroanthraquinone, gave only dark decomposition products, although the reactivity of the chlorine atom in this ester was demonstrated by its displacement with *p*-toluenesulfonamide.

EXPERIMENTAL

1-(2-Nitro-1-anthraquinonyl)-pyridinium chloride (II). A slurry of 1·44 g 1-chloro-2-nitroanthraquinone[7] (I) in 25 ml dry pyridine was heated rapidly to the boil. The resulting clear brown solution quickly deposited a yellow precipitate. The mixture was cooled and the solid was filtered and washed with pyridine and ethyl acetate. The yield of greenish-yellow product was 1·64 g (89·5%). Crystallization from a methanol–ethyl acetate mixture gave 1·20 g m.p. 214–216° d.

(Found: C, 61·70; H, 2·88; Cl, 9·85; N, 7·41; O, 17·63. Calc. for $C_{19}H_{11}ClN_2O_4$: C, 62·21; H, 3·00; Cl, 9·68; N, 7·43; O, 17·44%).

8H,13H-Anthra[1',2',4,5]imidazo[1,2-a]pyridine-8,13-dione (III). A mixture of 1·44 g I, 0·47 g 2-aminopyridine, a few mg cupric acetate and 10 ml glycol diacetate was stirred and boiled under reflux for 3 hr. A dark solid deposited and nitrous fumes were evolved. The mixture was cooled, and the solid was separated, washed with ethyl acetate and dried, giving 0·60 g of dark product. Vacuum sublimation afforded 0·25 g (16·8% yield) of orange needles m.p. >360°, which gave a red vat solution.

(Found: C, 76·47; H, 3·44; N, 8·94; O, 10·81. Calc. for $C_{19}H_{10}N_2O_2$: C, 76·50; H, 3·36; N, 9·40; O, 10·72%).

1-Amino-2-nitroanthraquinone (IV). A mixture of 5·80 g I, 5·00 g *p*-toluenesulfonamide, 1·70 g anhydrous sodium acetate, 0·50 g cuprous chloride and 150 ml amyl alcohol was stirred and heated at 125° for 6 hr, then was cooled, diluted with petroleum ether and filtered. The dry toluenesulfonamido derivative was dissolved in 50 ml conc H_2SO_4 and the solution warmed on a steam bath for ½ hr, then poured onto ice and filtered. The bright red solid was washed well and dried. Crystallization from acetic acid gave 4·05 g (72·5% yield) of red needles, m.p. 226–228°. A further crystallization from acetic acid raised the m.p. to 228–229·5° (lit[11] 223°).

(Found: C, 62·53; H, 2·85; N, 10·55; O, 24·28. Calc. for $C_{14}H_8N_2O_4$: C, 62·65; H, 3·01; N, 10. 45; O, 23·85%).

Antraquinone-1-diazo-2-oxide (V). To a solution of 3·00 g 1-amino-2-nitroanthraquinone in 10 ml H_2SO_4 was added 1·10 g powdered sodium nitrite. The solution was then heated at 60° for 6 hr. Dilution with ice gave 2·50 g (100% yield) or orange product, having $\lambda\lambda$ 4·70, 5·98 and 6·01 μ. As the diazo oxide proved sensitive to heat and light, it could not be purified for analysis.

(Found: C, 65·09; H, 2·55; N, 11·98. Calc. for $C_{14}H_6N_2O_3$: C, 67·20; H, 2·44; N, 11·20%).

N-Aminonaphthalimide. To a stirred solution of 10·0 g commercial naphthalic anhydride in 50 ml hot dimethylformamide, was added (as rapidly as the vigor of the reaction permitted) a solution of 5 ml 85% hydrazine hydrate in 10 ml dimethylformamide. A thick slurry formed immediately. The cold mixture was filtered and the solid was washed with ethanol and water, and dried. The yield was 8·97 g (84%) of yellow crystals, m.p. 262–264°. Crystallization from dimethylformamide raised the melting point to 264–266° (lit[13] 262°); λ_{max}^{EtOH} 236·5 and 333 mμ (log ε 4·63 and 4·13); $\lambda\lambda$ 3·00, 3·16 and 6·00 μ.

N,N-Naphthaloyl-N'-(2-nitro-1-anthraquinonyl)-hydrazine. A slurry of 1·50 g I, 1·25 g N-aminonaphthalimide,[11] 0·41 g sodium acetate, 0·10 g cuprous chloride and 75 ml amyl alcohol was stirred and boiled under reflux for 1·5 hr then cooled and filtered. The solid was crystallized from chlorobenzene to give 1·40 g (58% yield) of orange microneedles, m.p. 305–315°. A portion for analysis, recrystallized from chlorobenzene, melted at 314–315°.

(Found: C, 67·32; H, 2·66; N, 8·89. Calc. for $C_{26}H_{13}N_3O_6$: C, 67·39; H, 2·86; N, 9·08%).

10H, 15H, 16H, 18H-Anthra[2,1-e]benz[4,5]isoquinolo[2,1-b]-[1,2,4]triazine-10, 15, 18-*trione* (VI). To a solution of 2·0 g sodium sulfide nonahydrate in 40 ml pyridine and 60 ml water, was added 1·00 g N,N-naphthaloyl-N'-(2-nitro-1-anthraquinonyl)-hydrazine, and the mixture was boiled under reflux for 2 hr. The cooled mixture was filtered giving 0·60 g (66% yield) of blue solid, m.p. >360°. The product was purified by solution in sulfuric acid and precipitation with water.

(Found: C, 73·48; H, 2·95; N, 9·82; O, 12·63. Calc. for $C_{26}H_{13}N_3O_3$: C, 75·15; H, 3·15; N, 10·14; O, 11·56%).

N-Benzoyl-N′-(2-nitro-1-anthraquinonyl)-hydrazine (VII). A mixture of 2·88 g I, 1·60 g benzhydrazide and 150 ml amyl alcohol was stirred and boiled under reflux for 4 hr. The cooled mixture was filtered, giving 2·50 g (64% yield) of brown solid, m.p. 260–271°. Two crystallizations from acetic acid gave 1·90 g of golden felted microneedles m.p. 277–278° d.

(Found: C, 65·12; H, 3·18; N, 10·87; O, 20·46. Calc. for $C_{21}H_{13}N_3O_5$: C, 65·12; H, 3·38; N, 10·85; O, 20·65%).

Basic hydrolysis of VII. A slurry of 1·5 g VII in 60 ml methyl Cellosolve containing 0·50 g potassium hydroxide was stirred at 80° for ½ hr then was drowned and filtered, giving 0·90 g of deep red solid. Crystallization from acetic acid afforded 0·30 g of purple needles, m.p. 255–256° of *3-Phenyl-2H, 7H, 12H-anthra[1,2-e][1,3,4]oxadiazine-7,12-dione* (IX).

(Found: C, 74·01; H, 3·53; N, 8·70; O, 14·24. Calc. for $C_{21}H_{12}N_2O_3$: C, 74·08; H, 3·56; N, 8·23; O, 14·13%).

Dilution of the above acetic acid mother liquor with ligroin gave an orange product, which, after two crystallizations from amyl alcohol, melted at 245–246°, weighed 0·21 g and appears to be *1-(N′-Benzoyl-N-hydrazino)-2-(2-methoxyethoxy)-anthraquinone.*

(Found: C, 69·35; H, 4·93; N, 6·78; O, 18·74. Calc. for $C_{23}H_{22}N_2O_5$: C, 69·75; H, 5·15; N, 6·51; O, 18·59%).

3-Phenyl-1,4-dihydro-7H,12H-anthra[2,1-e][1,2,4]triazine-7,12-dione (X). A solution of 5·0 g sodium sulfide nonahydrate in 90 ml water was added to a solution of 1·00 g VII in 60 ml pyridine, and the slurry was stirred and boiled under reflux for 2 hr. The cooled mixture was diluted with water and filtered, giving 0·60 g (68% yield) of product. Crystallization from an acetic acid–water mixture yielded 0·36 g of deep blue X, m.p. 260–265° d.

(Found: C, 73·9; H, 3·79; N, 11·85. Calc. for $C_{21}H_{11}N_3O_2$: C, 74·2; H, 3·85; N, 12·37%).

3-Phenyl-7H,12H-anthra[2,1-e][1,2,4]triazine-7,12-dione (XI). A mixture of 0·20 g X, 15 ml glacial acetic acid and 5 drops of 40% peracetic acid was warmed slightly, whereupon the initial blue color changed to yellow. The mixture was diluted with water, and the product was filtered and crystallized twice from amyl alcohol, giving 0·11 g of yellow crystals, m.p. 255–257° d.

(Found: C, 74·84; H, 3·39; N, 12·55. Calc. for $C_{21}H_{11}N_3O_3$: C, 74·77; H, 3·29; N, 12·46%).

3-(1-Amino-2-anthraquinonyl)-1H,7H,12H-anthra[1,2-e][1,3,4]-oxadiazine-7,12-dione (XIII). A mixture of 2·10 g I, 2·00 g 1-aminoanthraquinone-2-carbohydrazide[16] and 150 ml dry *o*-dichlorobenzene was stirred at 160° for 6 hr. The cooled reaction mixture was filtered, giving 2·50 g (63·6% yield) of dull red XII (brown vat solution), m.p. ~340° d. No method was found to purify this hydrazide without converting it into XIII. Crystallization from pyridine and two recrystallizations from *o*-dichlorobenzene gave a 45% recovery of reddish-black (yellow-brown vat solution) XIII, m.p. >360°.

(Found: C, 71·33; H, 3·38; N, 8·99; O, 16·25. Calc. for $C_{29}H_{15}N_3O_5$: C, 71·74; H, 3·13; N, 8·66; O, 16·47%).

3-(1-Amino-2-anthraquinonyl)-1,4-dihydro-7H,12H-anthra[2,1-e][1,2,4]triazine-7,12-dione (XIV). A slurry of 3·00 g XII, 5·00 g sodium sulfide nonahydrate, 40 ml pyridine and 60 ml water was allowed to stir at room temp overnight. Filtration afforded 2·20 g of deep blue-black solid, m.p. >360°. A sample for analysis was crystallized from trichlorobenzene.

(Found: C, 71·98; H, 3·97; N,1 0·97. Calc. for $C_{29}H_{16}N_4O_4$: C, 71·89; H, 3·33; N, 11·57%).

3-(1-Amino-2-anthraquinonyl)-7H,12H-anthra[2,1-e][1,2,4]-triazine-7,12-dione (XV). Crystallization of XIV from nitrobenzene effected oxidation to XV, a burgundy-red solid with a light brownish-yellow vat.

(Found: C, 72·26; H, 2·94; N, 11·59. Calc. for $C_{29}H_{14}N_4O_4$: C, 72·19; H, 2·92; N, 11·61%).

3-Nitropyrazolanthrone (VIII). To a stirred solution of 2·87 g I in 50 ml dimethylformamide was added 1·20 ml 85% hydrazine hydrate. The reaction temperature rose to 40°, and after the mixture had been cooled, the product was filtered, giving brownish-yellow crystals m.p. 278–291°. Four crystallizations from amyl alcohol and two from glacial acetic acid gave 1·80 g (68% yield) of orange needles, m.p. 297–298°.

(Found: C, 63·33; H, 2·56; N, 15·88; O, 17·81. Calc. for $C_{14}H_7N_3O_3$: C, 63·40; H, 2·66; N, 15·84; O, 18·10%).

This product also was obtained when VII was warmed for ½ hr on the steam bath with sulfuric acid (0·3 g/15 ml), then diluted with water.

3-Aminopyrazolanthrone (XVI). To a solution of 3·61 g 2-benzamido-1-chloroanthraquinone[6] in 150 ml pyridine was added 2·80 ml 85% hydrazine hydrate, and the reaction was stirred and boiled under reflux for 4 hr. The fluorescent green solution was cooled, diluted with water and filtered, providing 2·90 g of dark brown solid. This was dissolved in 50 ml sulfuric acid and warmed for 1 hr on the steam bath, then the solution was cooled, diluted well with water and filtered, giving 1·90 g of orange-brown solid, m.p. 340–350°. Three crystallizations from aqueous ethanol afforded yellow-brown needles, m.p. 352–353° d.

(Found: C, 70·90; H, 4·15; N, 18·02. Calc. for $C_{14}H_9N_3O$: C, 71·48; H, 3·86; N, 17·86%).

This product (XVI) also was produced when either VII or XVIII was vatted and the vat solution was reoxidized and acidified.

3,3′-Azopyrazolanthrone (XVIII). To a solution of 2·87 g I in 50 ml dimethylformamide was added 5·70 ml 85% hydrazine hydrate. The reaction was heated at 130° for ½ hr, then was poured into water and filtered, giving 1·80 g of dark brown solid, m.p. >360°. Three crystallizations from nitrobenzene afforded 0·90 g (21·5% yield) of black powder, m.p. >360°, which dyed cotton a dark red from a deep blue vat.

(Found: C, 72·35; H, 3·28; N, 17·74; O, 6·76. Calc. for $C_{28}H_{14}N_6O_2$: C, 72·09; H, 3·03; N, 18·02; O, 6·86%).

2,2′-Dimethyl-3,3′-azopyrazolanthrone (XIX). A mixture of 0·50 g XVIII, 0·50 g sodium hydroxide, 5·0 ml methyl benzenesulfonate and 100 ml *o*-dichlorobenzene was stirred at 145° for 9 hr. The cooled solution was filtered and the solid was washed with ethanol and water, giving 0·35 g of dark solid (green vat solution), m.p. >360°. A sample for analysis was crystallized from nitrobenzene.

(Found: N, 17·13; Calc. for $C_{30}H_{18}N_6O_2$: N, 16·99%).

2-Nitro-3-(4-toluenesulfonamido)-anthraquinone. A mixture of 3·60 g 3-bromo-2-nitroanthraquinone (XX), 3·40 g *p*-toluenesulfonamide, 8·0 g anhydrous sodium acetate, 0·02 g cupric acetate and 60 ml methyl Cellosolve was stirred and boiled under reflux for 18 hr. The cooled reaction mixture was diluted with water and filtered, giving 3·60 g of solid, m.p. 182–187°. Crystallization from amyl alcohol followed by two recrystallizations from acetonitrile afforded 1·65 g of orange crystals, m.p. 207·5–212·5°.

(Found: C, 59·60; H, 3·32; N, 6·69. Calc. for $C_{21}H_{14}N_2O_6S$: C, 59·70; H, 3·32; N, 6·65%).

3-Amino-2-nitroanthraquinone. The above toluenesulfonamido derivative (1·45 g) was dissolved in 10 ml sulfuric acid and warmed gently (~50°) for 10 min. The cooled solution was diluted with water and filtered, giving 0·99 g of light yellow product, m.p. 297–302° d. Three crystallizations from chlorobenzene gave 0·47 g m.p. 307–310·5°. Recrystallization from pyridine gave 0·30 g of felted orange microneedles, m.p. 310·5–314° (lit[23,24] 316–317° and 305–306°).

1-(3-Nitro-2-anthraquinonyl)-pyridinium bromide (XXI). A solution of 1·16 g 2-bromo-3-nitroanthraquinone (XX) in 25 ml dry pyridine was boiled for a few minutes and cooled. Filtration yielded 1·10 g of crude product, which crystallized from methanol in tan needles (0·42 g), m.p. 244–245° d.

(Found: C, 55·89; H, 3·23; N, 7·08. Calc. for $C_{19}H_{11}BrN_2O_4$: C, 55·47; H, 2·67; N, 6·82%).

7H,12H-Anthra[2′,3′,4,5]imidazo[1,2-a]-pyridine-7,12-dione (XXII). A solution of 1·66 g XX 1·41 g 2-aminopyridine, and 0·04 g cupric acetate in 10 ml glycol diacetate was stirred and boiled under reflux for 18 hr. The cooled mixture was filtered, giving 1·35 g of brownish-yellow solid. Vacuum sublimation and two crystallizations from trichlorobenzene afforded 0·34 g of orange needles, m.p. >360°.

(Found: C, 76·30; H, 3·67; N, 10·04; O, 10·69. Calc. for $C_{19}H_{10}N_2O_2$: C, 76·50; H, 3·36; N, 9·40; O, 10·72%).

N,N-Naphthaloyl-N′-(3-nitro-2-anthraquinonyl)-hydrazine (XXIII). A mixture of 1·66 g XX, 1·10 g N-aminonaphthalimide, 0·41 g anhydrous sodium acetate, 0·25 g cuprous chloride and 60 ml amyl alcohol was stirred and boiled under reflux. Filtration of the cooled reaction mixture, and washing the solid with ethanol and water gave 2·17 g of crude solid. Crystallization (charcoal) from 1-chloronaphthalene or nitrobenzene afforded 1·20 g of fluffy yellow needles, m.p. >360°.

(Found: C, 67·38; H, 2·75; N, 9·12. Calc. for $C_{26}H_{12}N_4O_6$: C, 67·39; H, 2·86; N, 9·08%).

An attempt to convert this substance, by vatting, into the linear analog of compound VI gave (in 78% yield) only 2,3-diaminoanthraquinone, identified by microanalyses and by comparison of the infrared spectrum with that of an authentic sample.

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2,2'-Azoanthraquinone (XXIV). Hydrazine hydrate (1·14 ml of an 85% solution) was added to a slurry of 3·62 g XX in 50 ml dimethylformamide at 110°, and the resulting solution was stirred at this temp for 2 hr. The cooled solution was diluted with water and filtered, giving 2·34 g of brown solid. The solid was boiled with 15 ml acetic acid and filtered hot. The insoluble portion was extracted with a little hot dimethylformamide and filtered hot. The residue was crystallized from trichlorobenzene giving 0·15 g of tan solid, m.p. >350°.

(Found: C, 76·07; H, 3·01; N, 6·25; O, 14·49. Calc. for $C_{28}H_{14}N_2O_4$: C, 76·01; H, 3·19; N, 6·33; O, 14·47%).

The major product, isolated from the acetic acid extracts, was shown to be 2-amino-3-bromoanthraquinone by comparison with an authentic specimen.

N'-(2-Chloro-1-anthraquinonyl)-benzhydrazide. A solution of 0·72 g 2-chloro-1-nitroanthraquinone[7] and 0·50 g benzhydrazide in 10 ml dry pyridine was boiled under reflux for 6 hr, then most of the pyridine was allowed to boil away. The cooled residue was filtered, washed with methanol and dried. Crystallization from glycol diacetate afforded 0·49 g of bright yellow needles, m.p. ~ 256–264°, shown by infrared analysis to be a mixture of the product with the halonitro compound. Repeated crystallization from glycol diacetate gave the pure product, m.p. 278·5–279·5°; $\lambda\lambda$ 3·11, 6·02 and 6·10 μ.

(Found: C, 66·70; H, 3·51; Cl, 9·39; N, 7·56; O, 13·00. Calc. for $C_{21}H_{13}ClN_2O_3$: C, 66·91; H, 3·45; Cl, 9·43; N, 7·43; O, 12·75%).

3-Chloropyrazolanthrone. Crude N'-(2-Chloro-1-anthraquinonyl)-benzhydrazide (0·42 g, m.p. 256–264°) was dissolved in 10 ml conc H_2SO_4 and kept at 50° for 1 hr. The solution was diluted with water and filtered, and the resulting solid was crystallized from n-butanol, giving 0·21 g of yellow needles. The product was warmed with dil NaOHaq and the resulting red solution was filtered from an insoluble portion and acidified. The yellow precipitate was crystallized from chlorobenzene, giving 0·12 g of golden platelets, m.p. 285·5–286·5°.

(Found: C, 65·85; H, 2·89; N, 11·16. Calc. for $C_{14}H_7ClN_2O$: C, 65·95; H, 2·75; N, 11·00%).

6H,9H,14H-Anthra[1,2-d]pyrido[1,2-ap]yrimidine-6,9,14-trione (XXV). A solution of 0·75 g 1-chloro-2-carbomethoxyanthraquinone.[28] 0·25 g 2-aminopyridine and 0·01 g cupric acetate in 5 ml glycol diacetate was stirred and boiled under reflux for 3 hr. The mixture was cooled and filtered, giving 0·34 g of dark solid. Vacuum sublimation, then crystallization from trichlorobenzene gave 70 mg of brownish-orange needles, m.p. 336–338·5°; λ 5·98 and 6·02 μ. (poorly resolved).

(Found: C, 73·62; H, 2·81; N, 8·75. Calc. for $C_{20}H_{10}N_2O_3$: C, 73·61; H, 3·07; N, 8·59%).

2-Carbomethoxy-3-chloroanthraquinone. To a slurry of 5·73 g of 3-chloroanthraquinone-2-carboxylic acid [29] in 50 ml dichlorobenzene were added 3·5 ml thionyl chloride and 4 drops pyridine. The mixture was heated gently, producing a clear yellow solution, and the excess thionyl chloride was blown off by an air stream. Methanol (5 ml) was then added, the excess again being removed from the hot solution by a stream of air. The cooled solution was poured onto a 2 × 7 cm column of alumina, and developed with benzene. The effluent solution was stripped of solvents *in vacuo*, giving 4·38 g (73% yield) of crude ester, m.p. 151–153°. A sample for analysis was crystallized from acetonitrile in pale yellow needles, m.p. 154·5–155·5°.

(Found: C, 64·13; H, 3·01; Cl 11·60; O, 21·14. Calc. for $C_{16}H_9ClO_4$: C, 63·89; H, 2·95; Cl, 11·81; O, 21·25%).

2-Carbomethoxy-3-(4-toluenesulfonamido)-anthraquinone. A mixture of 1·52 g 2-carbomethoxy-3-chloroanthraquinone, 1·00 g *p*-toluenesulfonamide, 0·41 g anhydrous sodium acetate, 0·01 g cupric acetate and 5 ml methyl Cellosolve was stirred and boiled under reflux for 7 hr. The reaction mixture was cooled, and diluted with water. The resulting oil was washed with hot water, dissolved in benzene and chromatographed upon acid-washed[30] alumina. Evaporation of the eluate gave 0·65 g of golden platelets, m.p. 177–183°. Two crystallizations from acetonitrile gave 0·44 g of yellow crystals, m.p. 184–186°.

(Found: C, 63·23; H, 4·16; N, 2·99. Calc. for $C_{23}H_{17}NO_6S$: C, 63·45; H, 3·91; N, 3·22%).

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[29] F. Ullmann and I. C. Dasgupta, *Ber. Dtsch. Chem. Ges.* **47**, 553 (1914).
[30] K. R. Farrar, J. C. Hamlet, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 2657 (1952).

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STEROIDS—CXXVI[1]

SOME FISSION REACTIONS OF STEROID 5,6-EPOXIDES INDUCED BY BORON TRIFLUORIDE ETHERATE

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Abstract—Steroid 5α,6α-epoxides in dimethyl formamide solution undergo fission in the presence of boron trifluoride etherate with solvent participation to afford 5α-hydroxy-6β-formates. The mechanism of this and related reactions is discussed. In dimethyl sulphoxide and acetone the corresponding 5α,6β-diols are obtained.

5β,6β-Epoxides are much more resistant to boron trifluoride etherate in dimethyl formamide but when reaction occurs the product is the corresponding 5α,6β-diol.

In a series of alcohols, pregnenolone acetate-α-epoxide (Ia) upon reaction with boron trifluoride etherate afforded either the corresponding 5α-hydroxy-6β-alkyl ether or in the case of the branched C-3 to C-5 alcohols the 5α,6β-diol. In phenol solution 6β-phenoxypregnan-3β,5α-diol-20-one 3-acetate (XIX) was obtained. The conversion of the latter compound into 6α-phenoxyprogesterone (XXII) is described.

THE fission of steroid 5α,6α-epoxides with boron trifluoride etherate in benzene or benzene–ether solutions has been studied in great detail[3–11] and dependent upon the nature and stereochemistry of the substituents at C-3 either the C-6-ketone[3] (rings A–B *cis*) or the 6β-fluoro-5α-hydroxy-fluorohydrin[4–11] was obtained.

In an attempt to determine the mechanism of this very unusual reaction[12] we have investigated the fission of steroid 5,6-epoxides in reaction media other than benzene or benzene–ether mixtures. This paper describes some of our findings.

Initial experiments were carried out with 5α,6α-oxidopregnan-3β-ol-20-one acetate (Ia) and the reaction of this epoxide with boron trifluoride etherate in dimethyl formamide, dimethyl acetamide, dimethyl sulphoxide, acetone, a series of alcohols and phenol was investigated.

Treatment of a solution of Ia in dimethyl formamide with boron trifluoride etherate for 2 hours at room temperature followed by addition of water precipitated a fluorine free reaction product (IIa).[13] The possibility that simple hydrolytic cleavage had occurred to yield the 5α,6β-diol (IVa) was eliminated by a direct comparison

[1] Steroids—CXXV: J. A. Zderic and D. Chavez Limon, *J. Amer. Chem. Soc.* **81**, 4570 (1959).
[2] Taken in part from the thesis submitted by R. Urquiza to the Instituto Politécnico Nacional, México for the degree of Quimico Biólogo.
[3] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4596 (1957).
[4] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4765 (1957).
[5] A. Bowers and H. J. Ringold, *Tetrahedron* **3**, 14 (1958).
[6] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 4423 (1958).
[7] A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron* **7**, 138 (1959).
[8] A. Bowers, E. Denot, M. B. Sánchez and H. J. Ringold, *Tetrahedron* **7**, 153 (1959).
[9] J. S. Mills, A. Bowers, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 1264 (1959).
[10] J. A. Edwards, A. Zaffaroni, H. J. Ringold and C. Djerassi, *Proc. Chem. Soc.* 87 (1959).
[11] J. A. Zderic, D. Chavez Limon, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 3120 (1959).
[12] For an analysis of the electronic and conformational factors involved in the fission of 3β-hydroxy, 3-keto or 3-cycloethylene-ketal-5α,6α-epoxides with boron trifluoride etherate cf. refs. 4 and 7.
[13] In the absence of BF_3 the epoxide was recovered unchanged.

with an authentic sample, in turn prepared by aqueous perchloric acid[14] hydrolysis of the epoxide (Ia) in acetone solution.

Treatment of IIa with acetic anhydride in pyridine solution for 48 hours at room temperature led only to the recovery of starting material in good yield, indicating the absence of a secondary hydroxyl group. It was then treated with an excess of lithium aluminum hydride and the reduction product without purification was oxidized with 8 N chromic acid in acetone solution.[15] A compound was obtained in

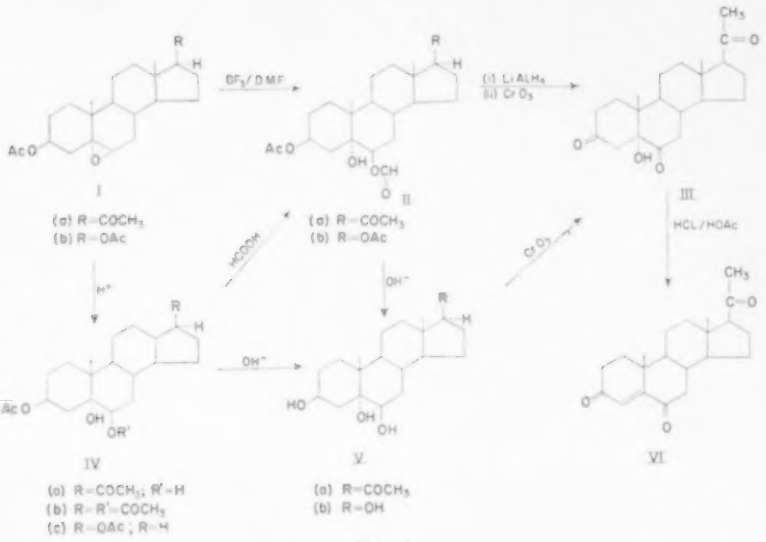


FIG. 1.

good yield which had strong carbonyl bands in the infrared at 1690 and 1718 cm^{-1} and also exhibited hydroxyl absorption at 3450 cm^{-1}. It showed no selective absorption in the ultraviolet and analyzed for $C_{21}H_{30}O_4$. Treatment of this compound with hydrogen chloride in acetic acid smoothly afforded 6-keto-progesterone[16] (VI), λ_{max} 250 mμ, log ε 4·00, identical in every respect with an authentic sample.[16b] This reaction sequence clearly established that the epoxide (Ia) cleaved to afford a C-6 oxygenated product and in view of its non-acylable nature it could best be formulated as a C-6 ester. A compound satisfying these requirements was the 5α-hydroxy-6β-formate (IIa), which upon lithium aluminum hydride reduction followed by oxidation would afford pregnan-5α-ol-3,6,20-trione (III). Acid catalyzed dehydration[17] would then yield 6-ketoprogesterone (VI). Indeed, alkaline hydrolysis of IIa afforded a triol (Va) identical with the product obtained from the alkaline hydrolysis of pregnan—3β,5α,6β-triol-20-one 3-acetate (IVa) and its derived diacetate (IVb). Also oxidation of the authentic triol (Va) with 8N chromic acid led to pregnan-5α-ol-3,6,20-trione (III) identical in every respect with the product obtained from compound IIa after

[14] F. Sondheimer, O. Mancera and G. Rosenkranz, *J. Amer. Chem. Soc.* **76**, 5020 (1954). These authors report a similar reaction in tetrahydrofuran solution.

[15] [a] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946); [b] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *Ibid.* 2548 (1953).

[16] [a] M. Ehrenstein, *J. Org. Chem.* **4**, 506 (1939); [b] C. Amendolla, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 1226 (1954).

[17] For analogous dehydrations with hydrogen chloride in acetic acid cf. refs. 5–10.

successive treatment with lithium aluminum hydride and chromium trioxide (II → III). The structure of compound IIa (pregnan—3β,5α,6β-triol-20-one 3-acetate 6-formate) was confirmed unambiguously when it was prepared in good yield by reaction of the triol monoacetate (IVa) with formic acid.[18]

The formation of a 6β-formate ester from a 5α,6α-epoxide can perhaps best be represented as a pseudo nucleophilic attack of dimethyl formamide[19] at C-6β in the manner shown in Fig. 2 (I → VII → II), the reaction being assisted by coordination

FIG. 2.

of electron deficient boron trifluoride with the epoxide oxygen atom. The aldimine type intermediate (VII) would be expected to hydrolyze readily in the presence of water[20] to afford the formate ester.[21]

Recently, two reports have appeared which lend credence to the idea that SN_2 attack by dimethyl formamide at electron deficient carbon atoms is not confined solely to 5α,6α-epoxides. Chang and Blickenstaff[22] have shown that a series of 3α or 3β-tosylates of saturated steroids were converted into their *epimeric* formates after treatment with dimethyl formamide at 78°. Similarly Paris and Hoffman[23] have obtained epi-estradiol ($\Delta^{1,3,5}$-estratriene-3β,17α-diol) by reacting the corresponding 17β-*tosylate* with potassium acetate in dimethyl formamide followed by an alkaline hydrolysis. Although the latter example is complicated by the addition of potassium acetate which conceivably could itself be the active displacing agent it should be pointed out that all previous attempts to displace a 17β-tosylate with acetate salts have been substantially unsuccessful.[24]

Walden inversion of this type can readily be explained on the basis of SN_2 attack at the carbon atom carrying the tosyloxy group to afford an aldimine type intermediate which reacts with water to generate the formate ester (Fig. 2) (VIII → IX → X). It is of interest to note that cholesterol tosylate affords cholesterol formate and not

[18] H. J. Ringold, B. Loken, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **78,** 816 (1956).

[19] The dimethyl formamide used for this work was carefully distilled immediately prior to use and was shown by titration with standard alkali to contain less than 0·0003 g/cc of formic acid.

[20] No vigorous attempts were made to dry the D.M.F. and S. R. Ross and M. M. Labes, *J. Amer. Chem. Soc.* **79,** 4155 (1957) report that even when D.M.F. is distilled over barium oxide it still contains 0·09–0·13% of water, more than the equimolar proportion needed for reaction. Thus the aldimine intermediate (VII) could either have been hydrolyzed during the time of the reaction or when water was added to precipitate the product.

[21] This mechanism was outlined by A. B. at the Steroids and Natural Products section of the Gordon Research Conference, August 1958.

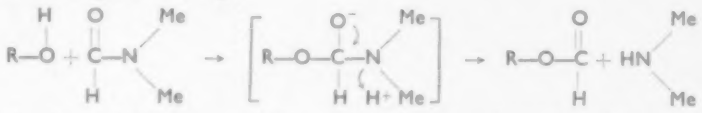
[22] F. C. Chang and R. T. Blickenstaff, *J. Amer. Chem. Soc.* **80,** 2906 (1958).

[23] A. A. Paris and C. Hoffman, *U.S. Pat.* 2,835,681.

[24] J. Elks and C. W. Shoppee, *J. Chem. Soc.* 241 (1953).

epi-cholesterol formate upon treatment with dimethyl formamide.[22] This is an expected result since it is well known that SN_2 type displacements at C-3 in cholesterol take place with an overall retention of configuration due to participation of the Δ^5-double bond.[25]

The direct formylation of a series of primary alcohols and cholesterol by iodine pentafluoride and dimethyl formamide has also been reported recently.[26] This reaction is probably of the same type and in the absence of double bond participation it should take place with inversion of configuration. Unfortunately, the author did not report a successful formylation of a secondary alcohol and in the absence of evidence to the contrary the possibility cannot be overlooked that formylation proceeded with retention of configuration, e.g.



A mechanism of this type could explain the formation of a 6β-formate from the BF_3-DMF fission of a 5α,6α-epoxide by assuming that the initial reaction is formation of the 5α,6β-diol and subsequent formylation at C-6 with retention of configuration. It was readily seen that this was not the case when IVa was recovered unchanged after treatment with boron trifluoride etherate in dimethyl formamide. Cholesterol was also stable to these reaction conditions.

FIG. 3.

The general applicability of the boron trifluoride–dimethyl formamide reaction to 5α,6α-epoxides was shown when a similar reaction with 5α,6α-oxidoandrostan-3β, 17β-diol diacetate (Fig. 1) (Ib) afforded the 6β-formate (IIb). Alkaline hydrolysis of IIb gave the same tetrol (Vb) as was obtained from the alkaline hydrolysis of the tetrol-diacetate (IVc). The latter compound was obtained in good yield by the aqueous perchloric acid fission[14] of Ib. Formic acid treatment of the tetrol diacetate (IVc) readily gave the 6β-formate (IIb) identical in every respect with the product from the boron trifluoride in dimethyl formamide treatment of Ib.

[25] S. Winstein and R. Adams, *J. Amer. Chem. Soc.* **70**, 838 (1948).
[26] T. E. Stevens, *Chem. & Ind.* 1090 (1958).

Extension of this reaction to a 3-cycloethylene ketal-5α,6α-epoxide led to a similar result, progesterone-bisketal-α-epoxide[27] (Fig. 3) (XI) yielding mainly pregnan—5α, 6β-diol-20-one 3-cycloethylene ketal 6-formate (XII), λ_{max}^{KBr} 3550 cm^{-1} (hydroxyl), 1725 and 1175 cm^{-1} (formate ester),[28] 1705 cm^{-1} (20-ketone) and 1125 cm^{-1} (ketal). In contrast to C-20, the cycloethylene ketal group at C-3 was stable to the conditions of the reaction. This marked difference in stability towards boron trifluoride of C-3 and C-20-ketal groups has been noted previously.[7]

In contrast to 5α,6α-epoxides the corresponding 5β,6β-epoxides were found to be much more resistant to cleavage by boron trifluoride etherate. For example, 5β,6β-oxidoandrostan-17β-ol 3-cycloethylene ketal acetate[7] (XIV) was recovered unchanged after 3 hours at room temperature with boron trifluoride etherate in dimethyl formamide and progesterone bisketal-5β,6β-epoxide (XV) underwent hydrolysis of the ketal group at C-20 to afford 5β,6β-oxidopregnan-20-one 3-cycloethylene ketal (XVI). However, pregnenolone acetate-5β,6β-epoxide[29] (XIII) under the same conditions was only recovered unchanged to the extent of 25 per cent, the corresponding 5α,6β-diol (IVa) being isolated in 36 per cent yield.

Replacement of dimethyl formamide with dimethyl acetamide in the boron trifluoride fission of pregnenolone acetate α-epoxide (Ia) led to the recovery of starting material and not to the 6β-acetate. Presumably steric factors inhibit the participation of dimethyl acetamide in a reaction of this type. However, in both dimethyl sulphoxide and acetone the room temperature treatment of the epoxide (Ia) with boron trifluoride etherate led to the 5α,6β-diol (IVa). Coordination of boron trifluoride with the epoxide oxygen followed by decomposition of this complex with water would afford the *trans*-diol (IVa).

FIG. 4.

[27] G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4112 (1957).

[28] The band at 1175 cm^{-1} is the C-O stretching vibration and is very characteristic for formate esters. The corresponding band of an acetate group lies between 1230 and 1250 cm^{-1} cf. L. J. Bellamy, *The Infrared Spectra of Complex Molecules* p. 161 Methuen, London (1956) and ref. 22.

[29] This compound was obtained by chromatography of the mother liquors from the preparation of Ia by the permonophthalic acid epoxidation of pregnenolone acetate. It was less polar towards alumina and had a specific rotation 32° more dextro-rotatory than Ia, in full accord with its assigned structure.[7]

The boron trifluoride induced fission of pregnenolone acetate α-epoxide was then investigated in a series of alcohols and with methanol and ethanol the corresponding 5α-hydroxy-6β-alkyl ethers (Fig. 4) (XVIIa) and (XVIIb) respectively were obtained. When isopropyl, *n*-butyl, tertiary butyl or tertiary amyl alcohol were used as solvents the product was the 5α-6β-diol (IVa), again emphasizing that substitution reactions at C-6β are sensitive to steric factors. However if the reaction was carried out in molten phenol at 50° the 6β-phenoxy ether (XIX) was obtained in fair yield and by appropriate manipulation it afforded 6α-phenoxyprogesterone (XXII). Mild alkaline hydrolysis of XIX gave the corresponding 3β-alcohol (XX) whence oxidation with 8 N-chromic acid led to the 5α-hydroxy-3-ketone (XXI). 6β-Substituted 5α-hydroxy-3-ketones are known to undergo elimination in the presence of small amounts of alkali with concomitant inversion of the 6β (axial) group to afford 6α-substituted-Δ^4-3-ketones[30] and in a like manner treatment of 6β-phenoxypregnan-5α-ol-3, 20-dione (XXI) with 0·25 per cent methanolic potassium hydroxide for 16 hours at room temperature gave 6α-phenoxyprogesterone (XXII).

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EXPERIMENTAL

Melting points are uncorrected. Rotations were measured in chloroform unless stated otherwise and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Dr. L. J. Throop and his staff for these measurements and for the infrared spectra which were obtained with a Perkin Elmer model 21 spectrophotometer with a sodium chloride prism. The elemental analyses were carried out by Dr. A. Bernhardt, Mülheim/Ruhr, Germany.

Treatment of pregnenolone acetate α-epoxide (Ia) *with boron trifluoride etherate in dimethyl formamide*

Boron trifluoride etherate (1·0 cc) (freshly distilled) was added to a solution of pregnenolone acetate epoxide (Ia, 500 mg) in dimethyl formamide[18,19] (20 cc) and kept at room temp for 4 hr. Addition of ice water and filtration afforded pregnan-3β,5α,6β-triol-20-one 3-acetate 6-formate (IIa, 450 mg), m.p. 195–201°, raised by one crystallization from acetone–hexane to 214–216°. The analytical sample from acetone–hexane had m.p. 215–217°, $[\alpha]_D$ ±0°. λ_{max}^{KBr} 3500,1757 (sh), 1730,1690 1250 and 1155 cm^{-1}. (Found: C, 68·58; H, 8·44 $C_{24}H_{34}O_6$ requires: C, 68·54; H, 8·63%). IIa (150 mg) was recovered unchanged after treatment with acetic anhydride (0·5 cc) in pyridine (5 cc) at room temp for 48 hr.

Conversion of IIa *into pregnan-5α-ol-3,6,20-trione* (III)

A solution of IIa (750 mg) in dry ether (75 cc) and tetrahydrofuran (75 cc) was added over 10 mins to a stirred suspension of lithium aluminum hydride (750 mg) in ether (100 cc). After 16 hr at room temp ethyl acetate was added to destroy the excess of reagent. Saturated sodium sulphate solution (15 cc) was then added followed by anhydrous sodium sulphate (approx 20 g). The inorganic salts were removed by filtration and the residue washed well with chloroform. Removal of the solvent from the combined filtrates afforded a product which was dissolved in acetone (300 cc) and cooled to 0°. An excess of 8 N-chromic acid[15] was then added and the solution kept at 0° for a further 2 mins. Addition of water and filtration afforded pregnan-5α-ol-3,6,20-trione (III, 435 mg), m.p. 265–271°, raised by crystallizations from aqueous pyridine to 278–280°, $[\alpha]_D$ +31° (pyridine), λ_{max}^{KBr} 3450, 1718 and 1690 cm^{-1}. (Found: C, 73·15; H, 8·60; O, 18·19. $C_{21}H_{30}O_4$ requires: C, 72·80; H,8·73; O, 18·47%).

Treatment of pregnan-5α-ol-3,6,20-trione (III) *with hydrogen chloride in acetic acid*

Dry hydrogen chloride was bubbled through a suspension of pregnan-5α-ol-3,6,20-trione (III, 250 mg) in acetic acid (20 cc) at 15–20° for 5 min when the flask was stoppered and kept at 20° for 4 hr. Addition of ice water and filtration afforded 6-ketoprogesterone (VI, 180 mg), m.p. 178–183° raised by crystallizations from acetone–hexane to 191–193°, undepressed on admixture with an authentic sample;[105] λ_{max}^{EtOH} 250 mμ, ε 10,000, $[\alpha]_D$ +30°.

[30] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 3091 (1958), and references cited therein.

Pregnan-3β,5α,6β-triol-20-one 3-acetate (IVa)

Perchloric acid (0·6 cc of 7%) was added to a solution of pregnenolone acetate α-epoxide (Ia, 750 mg) in acetone (25 cc). After 16 hr at room temp addition of ice water and filtration afforded pregnan-3β,5α,6β-triol-20-one 3-acetate (IVa, 690 mg) m.p. 214–222° raised by several crystallizations from acetone–hexane to 228–230°, $[\alpha]_D$ +36°. (Found: C, 70·12; H, 9·30; O, 20·82. $C_{23}H_{36}O_5$ requires: C, 70·37; H, 9·20; O, 20·50%).

Acetylation of IVa (pyridine–acetic anhydride/room temp/16 hr) afforded pregnan-3β,5α,6β-triol-20-one 3,6-diacetate (IVb), m.p. 215–217°, $[\alpha]_D$ ±0°. Lit[21] reports m.p. 212–215°, $[\alpha]_D$ −7° (Found: C, 69·17; H, 8·89; O, 22·04. Calc. for $C_{25}H_{38}O_6$: C, 69·09; H, 8·81; O, 22·10%).

Stability of IVa *to boron trifluoride etherate in dimethyl formamide*

Boron trifluoride etherate (0·1 cc) was added to a solution of IVa (50 mg) in dimethyl formamide (20 cc). After 4 hr at room temp addition of water and filtration afforded IVa identical in every respect with starting material.

Pregnan-3β,5α,6β-triol-20-one (Va)

(a) Potassium hydroxide (800 mg) was added to a solution of pregnan-3β,5α,6β-triol-20-one 3-acetate (IVa) in methanol (40 cc) and heated under reflux for 2 hr. After acidification with acetic acid and concentration to 10 cc addition of ice water precipitated pregnan-3β,5α,6β-triol-20-one (Va, 305 mg) m.p. 243–348° raised by several crystallizations from acetone–hexane to 253–255°, $[\alpha]_D$ +33° +32° (both in pyridine), $\lambda_{max}^{CHCl_3}$ 3438, and 1695 cm^{-1}. Lit[21] reports m.p. 252–255°, $[\alpha]_D$ +59° (pyridine). (Found: C, 71·85; H, 9·75; O, 18·15. Calc. for $C_{21}H_{34}O_4$: C, 71·96; H, 9·78; O, 18·26%).

(b) Alkaline hydrolysis of the diacetate (IVb) also afforded pregnan-3β,5α,6β-triol-20-one (Va) m.p. 250–253° identical in every respect with the product obtained from the preceding experiment.

Alkaline hydrolysis of pregnan-3β,5α,6β-triol-20-one 3-acetate 6-formate (IIa)

Potassium hydroxide (2·0 g) was added to a solution of IIa (1·0 g) in methanol (100 cc) and heated under reflux for 2 hr. After acidification with acetic acid the solution was concentrated to approximately 10 cc, when addition of ice water and filtration afforded pregnan-3β,5α,6β-triol-20-one (Va, 620 mg), m.p. 248–250°, raised by crystallizations from acetone–hexane to 251–253° undepressed on admixture with an authentic sample. The infrared spectrum was identical with the spectrum of the product obtained from the alkaline hydrolysis of IVa.

Oxidation of pregnan-3β,5α,6β-triol-20-one (Va)

The triol (250 mg) in acetone (60 cc) was treated with an excess of 8 N chromic acid[15] at 0° for 2–3 mins. Addition of water afforded a precipitate of pregnan-5α-ol-3,6,20-trione (III, 210 mg) m.p. 272–279°, raised by crystallization from aqueous pyridine to 278–280°, undepressed on admixture with the product described above (IIa → III), $[\alpha]_D$ +32° (pyridine). The infrared spectra were identical.

Formylation of pregnan-3β,5α,6β-triol-20-one 3-acetate (IVa)

The triol monoacetate (IVa, 500 mg) in formic acid (60 cc) was heated at 65° for 2 hr. After concentrating this solution to 20 cc *in vacuo* addition of ice water and filtration gave a product which after one crystallization from acetone–hexane afforded pregnan-3β,5α,6β-triol-20-one 3-acetate 6-formate (IIa, 310 mg.), m.p. 214–216° undepressed on admixture with the product obtained from the BF_3-D.M.F. fission of the epoxide (Ia → IIa), $[\alpha]_D$ ±0°. The infrared spectra of these two compounds were identical.

Androstan-3β,5α,6β,17β-tetrol 3,17-diacetate (IVc)

Perchloric acid (1·2 cc of 7%) was added to a solution of 5α,6α-oxidoandrostan-3β,17β-diol diacetate (Ib, 1·5 g) in acetone (50 cc). After 16 hr at room temp addition of water and extraction with ether gave a product which after one crystallization from acetone–hexane afforded androstan-3β,5α,6β,17β-tetrol 3,17-diacetate (IVc, 980 mg), m.p. 180–182°, raised by several crystallizations from

[21] O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.* **16**, 192 (1951).

acetone-hexane to 184–185°, $[\alpha]_D$ −44°; −41° (pyridine). (Found: C, 67·34; H, 9·11. $C_{23}H_{36}O_6$ requires: C, 67·62; H, 8·88%).

Androstan-3β,5α,6β,17β-tetrol (Vb)

Potassium hydroxide (1·0 g) was added to a solution of androstan-3β,5α,6β,17β-tetrol 3,17-diacetate (IVc, 500 mg) in methanol (50 cc) and heated under reflux for 2 hr. After acidification with acetic acid the solution was concentrated to a small volume when a saturated solution of sodium chloride was added and the product was extracted with ethyl acetate. The combined extracts were washed with a saturated solution of sodium chloride and dried over sodium sulphate. Removal of the solvent afforded androstan-3β,5α,6β,17β-tetrol (Vb), m.p. 249–257° raised by one crystallization from acetone–hexane to 259–261°, 310 mg. The analytical sample from acetone–hexane had m.p. 262–264°, $[\alpha]_D$ −14° (pyridine). (Found: C, 69·99; H, 10·07. $C_{19}H_{32}O_4$ requires; C, 70·33 H, 9·94%).

Androstan-3β,5α,6β,17β-tetrol 3,17-*diacetate* 6-*formate* (IIb)

(a) Boron trifluoride etherate (4·0 cc) was added to a solution of 5α,6α-oxidoandrostan-3β,17β-diol diacetate (Ib, 2·0 g) in dimethyl formamide (80 cc). After 2 hr at room temp addition of water and filtration afforded androstan-3β,5α,6β,17β-tetrol 3,17-diacetate 6-formate (IIb,1·78 g), m.p. 169–173°, raised by crystallizations from benzene–hexane to 182–184°, $[\alpha]_D$ −60°. Crystallization from aqueous methanol afforded a solvated form, m.p. 174–177°, λ_{max}^{KBr} 3500, 1748, 1730, 1245 and 1170 (broad) cm^{-1} (Found: C, 66·25; H, 8·24; O, 25·13. $C_{24}H_{36}O_7$ requires: C, 66·03; H, 8·31; O, 25·56%).

(b) Androstan-3β,5α,6β,17β-tetrol 3,17-diacetate (IVc, 0·5 g) in formic acid (60 cc) was heated at 65° for 2 hr. The solution was then concentrated to 20 cc *in vacuo*, when ice water was added precipitating the 6β-formate (IIb, 415 mg), m.p. 164–166°, raised by crystallizations from aqueous methanol to 173–176°, undepressed on admixture with a sample prepared by method (a); $[\alpha]_D$ −64° The infrared spectra of the two products were identical.

Alkaline hydrolysis of androstan-3β,5α,6β,17β-tetrol 3,17-*diacetate* 6-*formate* (IIb)

The 6β-formate (IIb; prepared as in method (a) above) was hydrolyzed with methanolic potassium hydroxide exactly as described for the hydrolysis of IVc → Vb. The product was androstan-3β,5α,6β, 17β-tetrol (Vb), m.p. 258–260°, undepressed on admixture with an authentic sample; $[\alpha]_D$ −16°. The infrared spectra were identical.

Treatment of 5α,6α-*oxidopregnan*-3,20-*biscycloethylene-ketal* (XI) *with boron trifluoride*

Boron trifluoride etherate (1·0 cc) was added to a solution of the α-epoxide[27] (XI, 1·0 g) in dimethyl formamide (20 cc). After 3 hr at room temp addition of water and filtration afforded a product which was adsorbed from benzene–hexane (50 : 50; 100 cc) onto alumina (40 g). Elution with benzene–hexane (50 : 50; 600 cc) afforded pregnan-5α,6β-diol-20-one-3-cycloethylene ketal 6-formate (XII, 390 mg) m.p. 160–163°, raised by crystallizations from acetone to 170–172°, $[\alpha]_D$ +14°; XII did not exhibit selective absorption in the ultraviolet; λ_{max}^{KBr} 3550, 1725, 1712 and 1180 cm^{-1} (Found: C, 68·75; H, 8·41; O, 22·71. $C_{24}H_{36}O_6$ requires: C, 68·54; H, 8·63; O, 22·83%).

Treatment of 5β,6β,-*oxidoandrostan*-17β-*ol*-3-*cycloethylene-ketal* 17-*acetate* (XIV) *with boron trifluoride*

Boron trifluoride etherate (1·5 cc) was added to a solution of the β-epoxide[7] (XIV, 1·5 g) in dimethyl formamide (30 cc). After 3 hr at room temp addition of water and filtration afforded a product (1·39 g) m.p. 144–148°, undepressed on admixture with starting material. After one crystallization from acetone it had m.p. 144–146°, $[\alpha]_D$ ±0°. Lit[7] records m.p. 146–148°,$[\alpha]_D$ −4°.

Treatment of 5β,6β-*oxidopregnan*-3,20-*biscycloethylene-ketal* (XV) *with boron trifluoride*

Boron trifluoride etherate (2·0 cc) was added to a solution of the β-epoxide[7] (XV, 1·5 g) in dimethyl formamide (25 cc). After 3 hr at room temp addition of water and isolation with ethyl acetate gave a product which was adsorbed from benzene–hexane (1 : 1; 200 cc) onto alumina (75 g). Elution with benzene (800 cc) afforded 5β,6β-oxidopregnan-20-one-3-cycloethylene-ketal (XVI, 590 mg), m.p. 153–159°, raised by crystallizations from ethyl acetate–methanol containing a trace of pyridine to 159–161°, $[\alpha]_D$ +88°, λ_{max}^{KBr} 1710 cm^{-1} (Found: C, 73·55; H, 9·15; O, 17·29. $C_{23}H_{34}O_4$ requires: C, 73·76; H, 9·15; O, 17·09%).

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5β,6β-Epoxidopregnan-3β-ol-20-one acetate (XIII)

The epoxidation of pregnenolone acetate (50 g) with permonophthalic acid (35 g) was carried out as described previously.[5] Crystallization of the product from methanol afforded 5α,6α-epoxidopregnan-3β-ol-20-one 3-acetate (31 g), m.p. 162–164° and a second crop (7·8 g) m.p. 117–165°. Evaporation of the mother liquors gave a noncrystalline product (10·5 g) which was adsorbed from hexane–benzene (70 : 30; 250 cc) onto alumina (350 g). Elution with hexane-benzene (1 : 1; 2 l.) and one crystallization from acetone–hexane gave 5β,6β-epoxidopregnan-3β-ol-20-one acetate (XIII, 3·25 g) m.p. 126–128°, raised by crystallizations from acetone–hexane to 137–139°, $[\alpha]_D$ +43°. (Found: C, 73·69; H, 9·27; O, 17·27. $C_{23}H_{34}O_4$ requires: C, 73·76, H, 9·15; O, 17·09%).

Treatment of 5β,6β-epoxidopregnan-3β-ol-20-one acetate (XIII) *with boron trifluoride*

Boron trifluoride etherate (0·5 cc) was added to a solution of 5β,6β-epoxidopregnan-3β-ol-20-one acetate (500 mg) in dimethyl formamide (10 cc) at room temp. After 3 hr at room temp addition of water and filtration afforded a product (450 mg) which was adsorbed from hexane–benzene (50 : 50; 100 cc) onto alumina (30 g). Elution with benzene (200 cc) gave starting material (125 mg) m.p. 133–136°, raised by one crystallization from acetone–hexane to 136–139° undepressed on admixture with an authentic sample. Further elution with benzene-ether (90 : 10; 600 cc) afforded pregnan-3β, 5α,6β-triol-20-one 3-acetate (IVa, 180 mg), m.p. 221–226° raised by crystallizations from acetone to 227–228°, undepressed on admixture with an authentic sample; $[\alpha]_D$ +38°. The infrared spectra of the two samples were identical.

6β-Methoxypregnan-3β,5α-diol-20-one 3-acetate (XVIIa)

Boron trifluoride etherate (1·0 cc) was added to a solution of 5α,6α-oxidopregnan-3β-ol-20-one 3-acetate (Ia, 500 mg) in methanol (20 cc). After 2 hr at room temp addition of water afforded a product which after one crystallization from acetone–hexane gave 6β-methoxypregnan-3β,5α-diol-20-one 3-acetate (XVIIa, 340 mg), m.p. 198–210° raised by crystallizations from acetone–hexane to 213–215°, $[\alpha]_D$ +20°, λ_{max}^{KBr} 3370, 1725, 1685 and 1245 cm^{-1} (Found: C, 71·13; H, 9·35; O, 19·25. $C_{24}H_{38}O_5$ requires: C, 70·90; H, 9·42; O, 19·68%).

6β-Ethoxypregnan-3β,5α-diol-20-one 3-acetate (XVIIb)

Repetition of the previous experiment with ethanol instead of methanol led to 6β-ethoxypregnan-3β,5α-diol-20-one 3-acetate (XVIIb, 470 mg), m.p. 168–170°, raised by crystallizations from acetone–hexane to 177–179°, $[\alpha]_D$ +17°, λ_{max}^{KBr} 3400, 1725, 1685 and 1243 cm^{-1} (Found: C, 71·58; H, 9·47; O, 18·69. $C_{25}H_{40}O_5$ requires: C, 71·39; H, 9·59; O, 19·02%).

When this experiment was carried out for 24 hr instead of 2 hr concomitant hydrolysis of the 3β-acetate occurred to afford 6β-ethoxypregnan-3β,5α-diol-20-one (XVIIc), m.p. 218–220°, $[\alpha]_D$ +38°. (Found: C, 73·02; H, 10·12; O, 16·91. $C_{23}H_{38}O_4$ requires: C, 72·97; H, 10·12; O, 16·91%).

Acetylation of XVIIc (acetic anhydride/pyridine/room temperature/24 hr) smoothly afforded XVIIb.

When the epoxide (Ia) was treated with boron trifluoride etherate as described above (Ia → XVIIa) in either acetone, dimethyl sulphoxide, isopropyl alcohol, t-butyl alcohol or t-amyl alcohol the product in good yield was pregnan-3β,5α,6β-triol-20-one 3-acetate (IVa).

In dimethyl acetamide Ia was recovered unchanged.

6β-Phenoxypregnan-3β,5α-diol-20-one 3-acetate (XIX)

Boron trifluoride etherate (4·0 cc) was added to a solution of pregnenolone acetate 5α,6α-epoxide (Ia, 4·0 g) in anhydrous phenol (20 g) at 50°. After 5 min at 50° water (300 cc) was added and sufficient 5% KOH solution to give an alkaline solution. The product was then extracted from this solution with ether (3 × 250 cc) and the combined ether extracts were washed well with water and dried over sodium sulphate. Removal of the solvent gave a product which was absorbed from benzene–hexane (1 : 1; 200 cc) onto alumina (200 g). Elution with benzene–hexane (80 : 20; 1500 cc) afforded 6β-phenoxypregnan-3β,5α-diol-20-one 3-acetate (XIX, 2·32 g), m.p. 165–169°, raised by one crystallization from methanol to 170–172° (1·85 g). The analytical sample from methanol had m.p. 172–174°, $[\alpha]_D$ −35°, λ_{max}^{EtOH} 222, 274 and 280 mμ, ε 9,500, 1350 and 1200 respectively; λ_{max}^{KBr} 3400, 1720, 1685, 1595, 1585 and 1240 cm^{-1} (Found: C, 74·42; H, 9·00; O, 16·75. $C_{29}H_{40}O_5$ requires: C, 74·32; H, 8·60; O, 17·08%).

Mild alkaline hydrolysis of XIX (1% methanolic potassium hydroxide/reflux 30 min) afforded 6β-phenoxypregnan-3β,5α-diol-20-one (XX). The analytical sample from acetone–hexane had m.p. 182–183, $[\alpha]_D$ ±0°, λ_{max}^{EtOH} 224, 274 and 280 mμ, ε 7590, 1180 and 978 respectively; λ_{max}^{KBr} 3450, 3300, 1690 and 1588 cm^{-1} (Found: C, 75·67; H, 9·05; O, 15·18. $C_{27}H_{38}O_4$ requires: C, 76·02; H, 8·98; O, 15,00%).

6β-Phenoxypregnan-5α-ol-3,20-dione (XXI)

An excess of 8 N chromic acid [18] (permanent orange color) was added to a solution of 6β-phenoxy-pregnan-3β,5α-diol-20-one (XX, 1·0 g) in acetone (50 cc) at 0°. After a further 2 min at 0° ice water was added and the precipitate of 6β-phenoxypregnan-5α-ol-3,20-dione (XXI), m.p. 213–220° was removed by filtration. One crystallization from acetone afforded 770 mg with m.p. 228–232°, raised by several crystallizations from acetone to 232–234°, $[\alpha]_D$ ±0°, λ_{max}^{EtOH} 222, 272 and 280 mμ, ε 8,300, 1260 and 980 respectively; λ_{max}^{KBr} 3400, 1703, 1685, 1588 and 1575 cm^{-1} (Found: C, 76·14; H, 8·53, O, 15·80. $C_{27}H_{36}O_4$ requires: C, 76·38; H, 8·55; O, 16·07%).

6α-Phenoxyprogesterone (XXII)

Potassium hydroxide (200 mg) in methanol (4·0 cc) was added to a solution of 6β-phenoxy-pregnan-5α-ol-3,20-dione (XXI, 500 mg) in methanol (30 cc) and heated under reflux in a nitrogen atmosphere for 30 min. After neutralizing the solution with acetic acid it was evaporated to a small volume when addition of water afforded a precipitate which was removed by filtration and adsorbed from hexane–benzene (80 : 20; 50 cc) onto alumina (25 g). Elution with benzene–hexane (70 : 30; 400 cc) afforded 6α-phenoxyprogesterone (XXII, 250 mg) m.p. 95–100°, raised by crystallizations from aqueous methanol to 108–110°, $[\alpha]_D$ +114°, λ_{max}^{EtOH} 222 mμ, ε 15,000; λ_{max}^{KBr} 1690, 1665, 1615 and 1585 cm^{-1} (Found: C, 79·37; H, 8·66; O, 11·62. $C_{27}H_{34}O_3$ requires: C, 79·76; H, 8·46; O, 11·78%).

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STERIC CORRELATIONS BY THE QUASI-RACEMATE METHOD

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Abstract—The quasi-racemate method for steric correlation of optically active compounds is presented and discussed. The work performed in this field by the Uppsala school is reviewed with special reference to the correlation of the amino acids and the terpenes to the glyceraldehyde system.

KNOWLEDGE of the steric relationships is indispensible for the understanding of many reaction mechanisms, not least in biological systems, and also for the theory of optical activity. The work in this field has attracted renewed interest since the problem of the absolute configuration has been solved. From the chemist's point of view, the optical activity in itself is perhaps of secondary interest; it is important as a physical constant for characterizing a compound, but the main interest is attached to the geometrical form of the molecules, which often exerts a decisive influence on the possibilities of reaction in asymmetric systems. The quasi-racemate method, which is based on the power of the asymmetric molecules to form molecular compounds or solid solutions must not be regarded only as a control or a complement to the classical methods. It also offers possibilities for the development and deepening of our knowledge of reactions in asymmetric systems.

It is well known that a pair of enantiomorphs often crystallize together to give a racemic compound, a true racemate, which manifests itself in the melting-point diagram as a special curve branch with a maximum at 50 per cent. The enantiomorphs seldom give a continuous series of solid solutions (a pseudo-racemate) or a eutectic mixture (a conglomerate). The true racemate is a molecular compound, characterized by a special crystal lattice, where the (+)- and (−)-molecules occupy different positions; often they are arranged in pairs having a centre of symmetry. In this way the lattice obtains a higher symmetry and a higher stability than when the enantiomorphs crystallize separately.

Centnerzwer reported[1] that (+)-chlorosuccinic acid and (−)-bromosuccinic acid give a molecular compound in the ratio 1 : 1, which must be regarded as a kind of racemate. Delépine independently took up the question of the existence of such molecular compounds for general discussion[2] and later Timmermans realized that they could be utilized for studying steric relationships.[3] In older literature, different names were used for such compounds, but now the term quasi-racemate or quasi-racemic compound, introduced by the present author,[4] seems to be generally accepted.

A quasi-racemate may thus be defined as a molecular compound, which can be derived from a true racemate by a not too extensive change in the structure of one of the components. Like a true racemate it manifests itself in the melting point diagram

[1] M. Centnerszwer, *Z. Physik. Chem.* **29**, 715 (1899).
[2] M. Delépine, *Bull. Soc. Chim. Fr.* [4] **29**, 656 (1921).
[3] J. Timmermans, *Rec. Trav. Chim.* **48**, 890 (1929).
[4] A. Fredga, *The Svedberg 1884 30/8 1944* p. 261. Uppsala and Stockholm (1944).

as a special curve branch with a maximum at 50 mole-per cent, but as the components have different melting-points, the diagram is not symmetrical. Its formation is of course due to the tendency to form a more symmetrical and more stable lattice. Some aspects on this question have been discussed by Hägg.[5]

The possibilities for the formation of a quasi-racemate may depend upon a number of factors. Already the tendencies to form true racemic compounds may be very different, even for closely related substances, and it is obvious that both sterical and polar factors must be taken into consideration. It is sometimes stated that strong

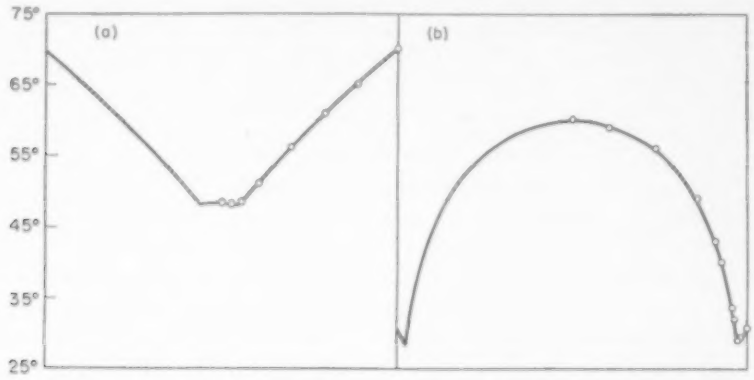


FIG. 1. (a) (+)- and (−)-Ethylxanthopropionic acid.
(b) (+)- and (−)-Ethylxantho-n-butyric acid.

polar forces are necessary for the formation of true racemates,[6,7] and this may be true to a certain extent, but in the author's opinion the influence of this factor is somewhat overrated. For instance, Matell has found[8] that the methyl ester of the β-phenyl-β-hydroxy-pivalic acid gives a true racemate while the free acid is a eutectic mixture of the enantiomorphs; from experience, the ester should be less polar than the acid. The present author has examined two homologues, α-ethylxanthopropionic acid and α-ethylxantho-n-butyric acid, where the polar forces must be very similar in nature.[4] In the first case (Fig. 1a), the racemate melts considerably lower than the enantiomorphs and only indicates its presence within a very limited part of the diagram. The higher homologue behaves in an opposite manner, the molecular compound completely dominating the diagram (Fig. 1b).

It is difficult to give an adequate measure of the racemate-forming tendency; it would be more correct to express it in terms of energy, but the determination of the energy changes in question is very laborious, especially as the enantiomorphs are often accessible only in small quantities. For practical purposes, one can often use the difference in melting point between the racemate and the enantiomorphs; a high melting-point of the racemate means a stable molecular compound. Pettersson has pointed out[9] that the extent of the middle branch of the curve or the height of the maximum, reckoned from the eutectic points (compare Fig. 1a and b) may be used as a measure of the racemate forming tendency.

[5] G. Hägg, *The Svedberg 1844 30/8 1944* p. 140. Uppsala and Stockholm (1944).
[6] P. Landrieu, *Bull. Soc. Chim. Fr.* [4] **31**, 1217 (1922).
[7] J. D. M. Ross and I. C. Sommerville, *J. Chem. Soc.* 2770 (1926).
[8] M. Matell, *Arkiv. Kemi* **1**, 455 (1950).
[9] K. Pettersson, *Arkiv. Kemi* **10**, 297 (1956).

It seems justified to assume that a substance, which forms a very stable true racemate, should also have a strong tendency to form quasi-racemates, and from experience this assumption holds good.

It may be asked how great the structural difference between the two components may be, that the power of forming quasi-racemates may not be lost. A first indication is given by the power of different atoms or atomic groups to replace one another in isomorphous mixtures. It has been found, however, that quasi-racemates are obtained in many cases, where the enantiomorphs of analogous configuration are not isomorphous. In several cases, quasi-racemates were obtained between the lowest optically active members of homologous series. Also a hydrogen atom in one of the components may be replaced by bromine or iodine[10] if the molecule is not too small.

In many cases, the question arises, whether a molecular compound between two optically active substances is really to be considered as a quasi-racemate. In the first place, it is necessary to make clear which atoms or groups in the two components should be regarded as corresponding to each other. Also, each component should form a molecular compound only with one antipode of the other. If compounds are formed with both antipodes (which is very unusual) the case must be examined very thoroughly. In addition, crystallographic relationships should be sought for between the quasi-racemate and the true racemates of the components. It may even happen, that the quasi-racemate is isomorphous with an unstable form of one of the true racemates. It is often simpler to investigate, with the aid of melting-point curves, if the quasi-racemate forms solid solutions with one of the true racemates, but X-ray diagrams may often render good service. The X-ray methods are also very useful if the quasi-racemates melt incongruently (maximum overlapped by a descending curve branch as in Fig. 13) or when the components tend to decompose or racemise on heating.

In special cases, other physico-chemical methods may be resorted to (solubility determinations, examination of crystals under the polarising microscope etc.). Rosenberg and Schotte have found that a quasi-racemate may give rise to special frequencies in the I.R.-spectrum of the solid phase.[11]

If two compounds are too different in structure to give a quasi-racemate, the question of configuration may be solved by comparing both with a suitably chosen third substance. Another method is to introduce a common substituent in both substances (without affecting the centre of asymmetry); the structural difference is thus rendered less prominent. Similar methods may be employed if the two compounds, on account of their physical properties (low melting-point, poor crystallization power etc.) do not lend themselves to the recording of melting point diagrams. For instance, low-melting acids may be studied as amides.[12,13]

In cases, where no quasi-racemate is formed, it may happen that the antipodes with corresponding configuration give solid solutions (mixed crystals), easily detectable in the melting point diagram. If finally an optically active substance gives curves of the common eutectic type with both enantiomorphs of another, though a quasi-racemate could be expected, these diagrams are rather similar but in most cases not quite identical. It seems that if there is a difference, the eutectic temperature is always

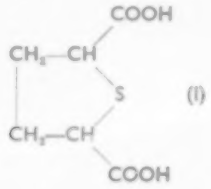
[10] A. Fredga, To be published.
[11] A. Rosenberg and L. Schotte, *Arkiv. Kemi* **8**, 143 (1955).
[12] K. Mislow and M. Heffler, *J. Amer. Chem. Soc.* **74**, 3668 (1952).
[13] K. Pettersson, *Arkiv. Kemi* **9**, 509 (1956); **10**, 283 (1956).

lower when the components have opposite configurations. The experimental material is, however, too small to permit any definite conclusions.

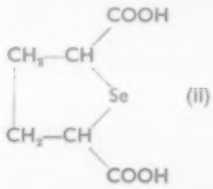
Timmermans, who in 1929 drew attention to this method of correlating configurations, has investigated a great number of systems and also reviewed the work in this field up to 1951.[14] In recent years, very interesting contributions have been made by Mislow *et al.*, who have, among other things, investigated atropisomeric substances.[12,15,16] The present article deals with the work performed in Uppsala and gives examples of the mode of procedures in different cases.

Organic compounds of sulphur and selenium

It is well known that analogous compounds of sulphur and selenium are often isomorphous and a number of such pairs have been tested in 1934–1943.[17] In some cases the enantiomorphs with corresponding configuration were isomorphous, in others they were not, but in all cases quasi-racemates were obtained. For such compounds, the method is thus very appropriate and the steric correlation presents no difficulties. As an example, the diagrams for the acids I and II are given. In



(I)



(II)

the first case, the racemate melts lower than the enantiomorphs (Fig. 2a), in the second much higher (Fig. 2b). The curve representing the quasi-racemate (Fig. 2c) looks like a sort of compromise between the two types. Such curves of intermediate type are often obtained when the components of the quasi-racemate are closely related in structure; another example is found in Fig. 11. When the structural difference is greater, the quasi-racemate may manifest itself only within a very limited part of the diagram, even if both components display a strong tendency to form true racemates.

Amino acids

The steric connections of hydroxy- and amino acids were studied (1924–1935) by Freudenberg and collaborators,[18] who made use of optical methods ("Verschiebungsregel"). They concluded that the naturally occurring amino acids most probably possess L-configuration. The quasi-racemate method seems not directly applicable for the correlation of these acids; they are too unlike in respect of the polar properties. Most amino acids occur in the crystal lattice as zwitter-ions and melt with decomposition, and a molecular compound between an amino and a hydroxy acid could be interpretable as a salt. By the introduction of a suitably chosen common substituent at the hydroxy and amino groups, however, it is possible to increase the structural

[14] J. Timmermans, *J. Chim. Phys.* **49**, 162 (1953).
[15] K. Mislow, *Trans. New York Acad. Sci.* [II] **19**, 298 (1957).
[16] K. Mislow and W. C. Meluch, *J. Amer. Chem. Soc.* **78**, 5920 (1956); K. Mislow and M. Siegel, *Ibid.* **80**, 473 (1958).
[17] A. Fredga, *Arkiv. Kemi, Mineral. Geol.* **11B**, No. 43 (1934); **12B**, No. 22 (1936); **12A**, No. 27 (1938); **17A**, No. 17 (1943). *Svensk Kem. Tid.* **49**, 124, 139 (1937); *J. Prakt. Chem.* [2] **150**, 124 (1938).
[18] K. Freudenberg and F. Rhino, *Ber.* **57**, 1547 (1924); K. Freudenberg and A. Noë, *Ibid.* **58**, 2399 (1925); K. Freudenberg and M. Meister, *Liebigs Ann.* **518**, 86 (1935).

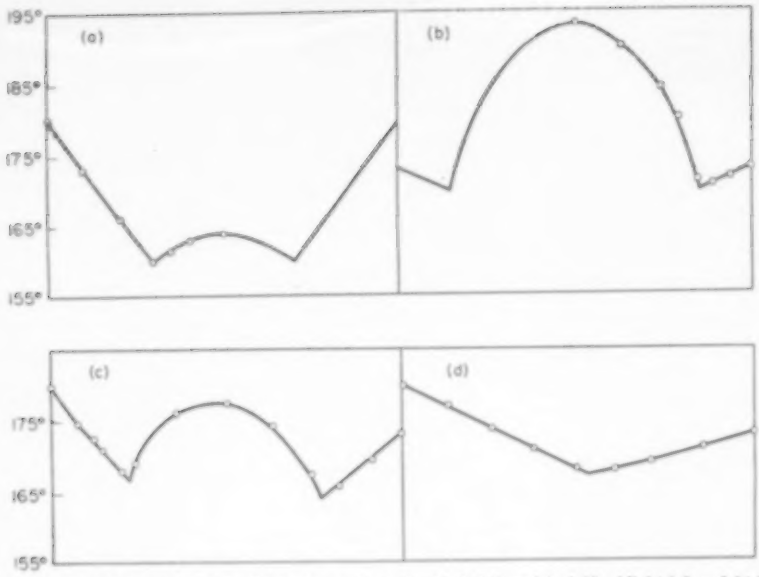
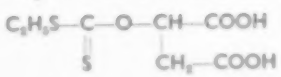
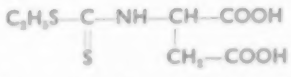


FIG. 2. (a) (+)- and (−)-I. (b) (+)- and (−)-II. (c) (+)-I and (−)-II. (d) (+)-I and (+)-II.

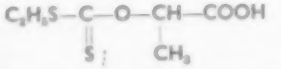
FIG. 3. (a) (+)-III and (−)-IV. (b) (+)-III and (+)-IV.

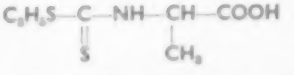
similarity of the molecules and at the same time suppress the basic character of the amino group. For the correlation of malic acid and aspartic acid, the author selected the compounds III and IV, which are easily prepared from the parent acids without


(III)


(IV)

affecting the centres of asymmetry. The melting point diagrams (Fig. 3) are very typical: in one case a quasi-racemic compound and in the other a curve indicating far-reaching miscibility in the solid state.[19] From the diagrams, it could be deduced that L-(−)-malic acid and natural(+)-aspartic acid have corresponding configurations. In the same manner, it was established, with the aid of the acids V and VI,[20] that L-(+)-lactic acid has the same configuration as natural (+)-alanine (Fig. 4). In this


(V)


(VI)

case, the acids with the same configuration give a curve of the common eutectic type.*

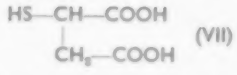
* Matell has later found that also the 2,4-dinitrophenyl group can be used as common substituent for correlating alanine and lactic acid.[19]

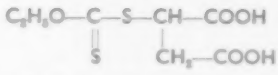
[19] A. Fredga, *Svensk Kem. Tid.* **53**, 221 (1941).
[20] A. Fredga, *Svensk Kem. Tid.* **54**, 26 (1942).

As expected, the results were in accordance with those obtained by Freudenberg, and the configuration of the amino acids could thus be regarded as definitely settled. Later the problem attracted renewed interest and additional evidence was produced by several authors.[21]

Mercaptosubstituted acids

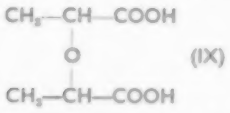
The conditions for a direct comparison between hydroxy and mercapto acids are not very favourable. The atomic radii of oxygen and sulphur are too unlike and the difference in the external dimensions of the molecules is thus rather great. For the correlation of malic acid and mercaptosuccinic acid (VII), two derivatives were selected, *viz.* the acid III mentioned above and the ethylxantho-succinic acid (VIII). The acids III and VIII are isomeric and differ only in the relative positions of a

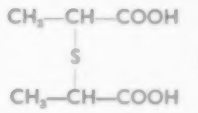

(VII)

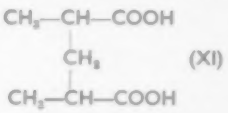

(VIII)

sulphur and an oxygen atom. Fig. 5 shows that the acids with the *same* direction of optical rotation give a quasi-racemate and must therefore be assigned *opposite* configurations. The acid VIII is easily connected to VII by chemical methods, and the final result was that malic acid and mercaptosuccinic acid with the same direction of rotation have also the same configuration.[22]

Lactic acid and α-mercaptopropionic (thiolactic) acid, which have low melting points, were correlated with the aid of two derivatives, dilactic acid (IX) and thiodipropionic acid (X). These acids gave certainly no molecular compounds, but since


(IX)


(X)


(XI)

the atomic radius of carbon lies between those of oxygen and sulphur, it might be expected that both acids would give quasi-racemates with αα′-dimethylglutaric acid (XI). The latter acid has a very strong tendency to racemate formation and in addition it forms so-called anomalous racemates, i.e. compounds between the enantiomorphs in other ratios than 1 : 1. (−)-Dilactic acid and (+)-dimethylglutaric acid gave a quasi-racemate (Fig. 6) but also a compound in the ratio 3 : 1 (75 per cent of dimethylglutaric acid.) The thiodipropionic acid gave under the same conditions a very pronounced maximum at 50 per cent and another molecular compound, represented by a very small curve branch in the vicinity of one of the eutectics. The composition of this compound, which melts incongruently, could not be derived from the diagram, but probably it is an analogue of the compound 3 : 1 mentioned above. The final result was, that L-(+)-lactic acid and (−)-α-mercaptopropionic acid have analogous configurations.[23]

The dimethylglutaric acid could also be correlated to the monomethylglutaric acid,[24] and even in this case a compound in the ratio 3 : 1 is formed in addition to the normal quasi-racemate (Fig. 7).

[21] P. Brewster, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature, Lond.* **166**, 178 (1950); D. P. Shoemaker, J. Donohue, V. Schomaker and R. B. Corey, *J. Amer. Chem. Soc.* **72**, 2328 (1950).
[22] A. Fredga, *Arkiv. Kemi, Mineral. Geol.* **14B** nr. 27 (1941).
[23] A. Fredga, *Arkiv. Kemi, Mineral. Geol.* **14B** nr. 12 (1940).
[24] A. Fredga, *Arkiv. Kemi, Mineral. Geol.* **24A** nr. 32 (1947).

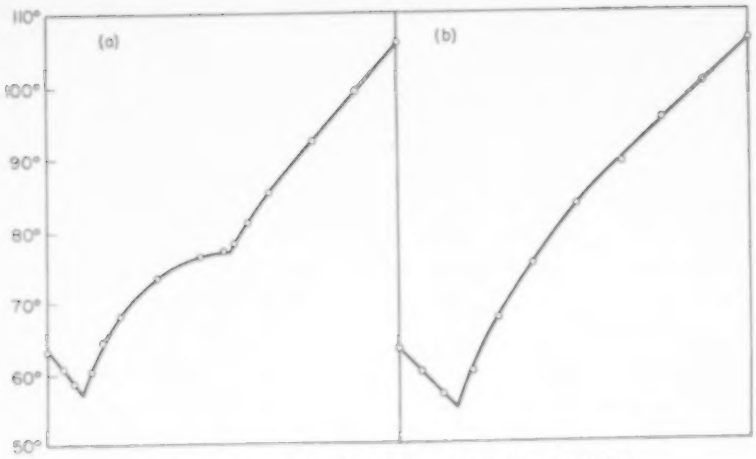


FIG. 4. (a) (+)-V and (+)-VI. (b) (−)-V and (+)-VI.

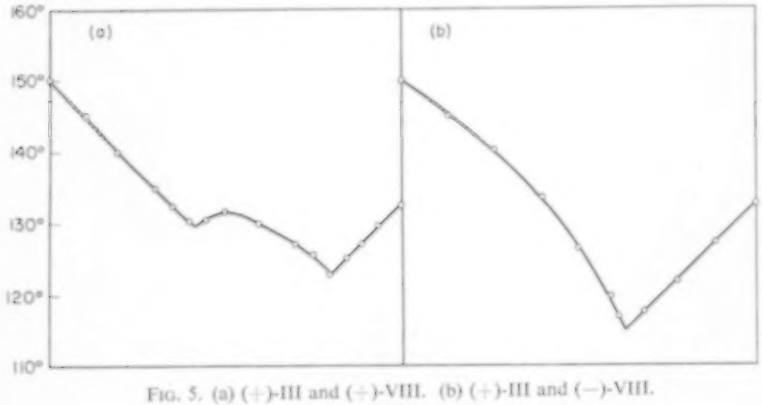


FIG. 5. (a) (+)-III and (+)-VIII. (b) (+)-III and (−)-VIII.

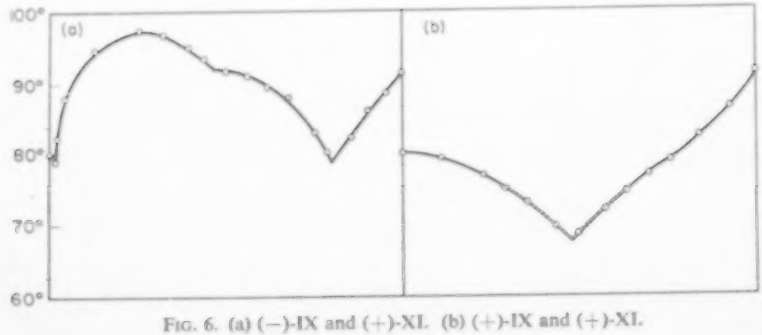
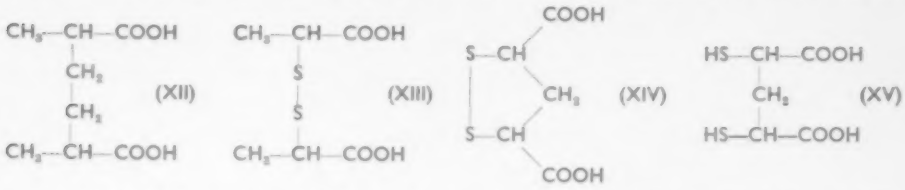


FIG. 6. (a) (−)-IX and (+)-XI. (b) (+)-IX and (+)-XI.

Attempts to correlate αα′-dimethyladipic acid (XII) and dithiodipropionic acid (XIII) met with no success.[25] Probably these acids have rather different conformations on account of the dihedral angle of the disulphide group which is about 90°. In the



cyclic acid XIV investigated by Schotte, the ring must tend to assume a planar conformation and the dihedral angle must be much smaller than usual (X-ray studies on another acid with the same ring indicate[26] that it is about 20°). It is interesting

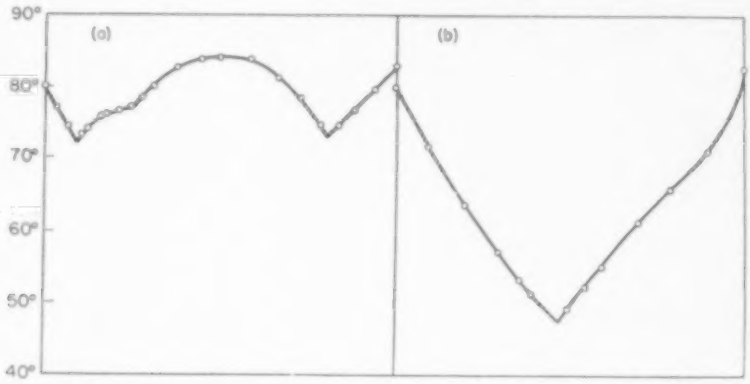


FIG. 7. (a) (−)-Dimethylglutaric acid (XI) and (+)-methylglutaric acid.
(b) (−)-Dimethylglutaric acid and (−)-methylglutaric acid.

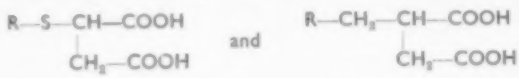
to note that in this case a quasi-racemate is obtained with the thiophane-dicarboxylic acid (I) mentioned earlier. On reduction, the acid XIV gives αα′-dimercaptoglutaric acid (XV) which by quasi-racemate formation was connected to dimethylglutaric acid (XI). The acids I and XIV could thus be connected to the glyceraldehyde system.[27]

Alkylsuccinic acids

It is known that CH_2 and S in organic compounds may replace each other in isomorphous mixtures, and we have seen above that they can do it in quasi-racemate formation. Mercapto succinic acid was thus tested against methylsuccinic acid and the enantiomorphs with opposite directions of rotation gave a compound 1:1 (Fig. 8a). Acids of the same mode of rotation gave a diagram indicating mutual but not unlimited miscibility in the solid state (Fig. 8b); obviously we have in the latter case a curve of the kind designated by Roozeboom as type 4. It is interesting to note that the two racemic acids give a very similar diagram indicating solid solutions.[28]

[25] I. Hedlund, *Arkiv. Kemi* **8**, 89 (1955).
[26] O. Foss and O. Tjomsland, *Acta Chem. Scand.* **11**, 1426 (1957).
[27] L. Schotte, *Arkiv. Kemi* **9**, 441 (1956).
[28] A. Fredga, *Arkiv. Kemi, Mineral. Geol.* **15B**, No. 23 (2942).

Matell[29] has extended this investigation to acids of the types:



where R represents n-alkyl groups from CH_3 to C_5H_{11}. For R = CH_3 he obtained curves very similar to those in Fig. 8. With growing chain length, the tendency to form quasi-racemates decreases and from R = C_4H_9 no molecular compounds were formed. An explanation for this behaviour cannot be given as yet. It is also remarkable that no quasi-racemate was obtained for *R* = iso-C_3H_7.

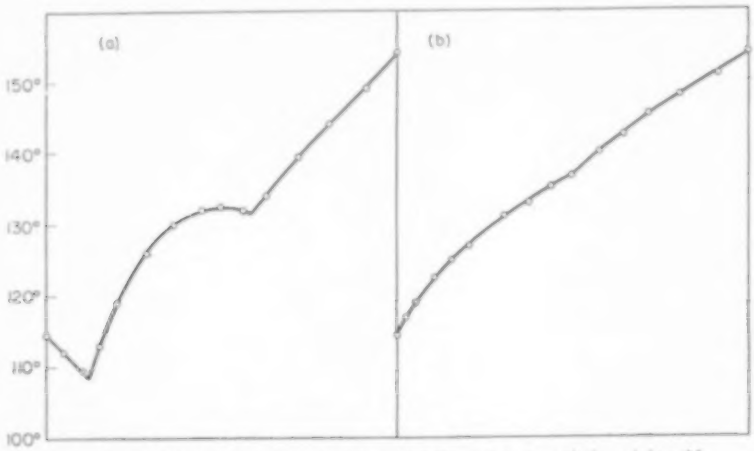


FIG. 8. (a) (+)-Mercaptosuccinic acid (VII) and (−)-methylsuccinic acid.
(b) (+)-Mercaptosuccinic acid and (+)-methylsuccinic acid.

The lower alkylsuccinic acids were thus correlated to the alkyl-sulphide–succinic acids, and the latter acids were easily connected with mercaptosuccinic acid by direct synthesis. The relative configurations of the alkylsuccinic acids could further be checked by quasi-racemate formation between adjacent members of the homologous series, and in this way also the n-pentyl- and n-hexylsuccinic acids could be correlated. As expected all alkylsuccinic acids with the same mode of rotation have the same configuration.

Investigations by the present author and collaborators[30,31] show that alkylsuccinic acids with branched alkyl groups can be connected to the unbranched acids and Porath found it possible to connect α-methyl-α-ethyl-succinic acid[32] and α-methyl-α-isopropyl-succinic acid.[33] To the author's knowledge, the latter acid represents the first correlation of an asymmetric quaternary carbon atom to the system of glyceraldehyde.

Halosuccinic acids

Several cases are known, where a methyl group can replace chlorine or bromine in isomorphous mixtures. When optically active methylsuccinic acid is mixed with

[29] M. Matell, *Arkiv. Kemi* **5**, 17 (1952).
[30] A. Fredga and U. Sahlberg, *Arkiv. Kemi, Mineral. Geol.* **18A** nr. 16 (1944).
[31] A. Fredga and E. Leskinen, *Arkiv. Kemi, Mineral. Geol.* **19B** nr. 1 (1944).
[32] J. Porath, *Arkiv. Kemi* **3**, 163 (1951).
[33] J. Porath, *Arkiv. Kemi* **1**, 385 (1949).

halosuccinic acid of *opposite* mode of rotation, the melting point sinks towards a eutectic (Fig. 9a and c). If, on the other hand, halosuccinic acid of the *same* mode of rotation is added, the melting point rises, indicating that the halosuccinic acid enters into solid solution (Fig. 9b and d). We have here diagrams of Roozeboom's type 4, and it is justified to conclude that the antipodes, which form solid solutions have corresponding configuration.[4] The non-appearance of quasi-racemic compounds in

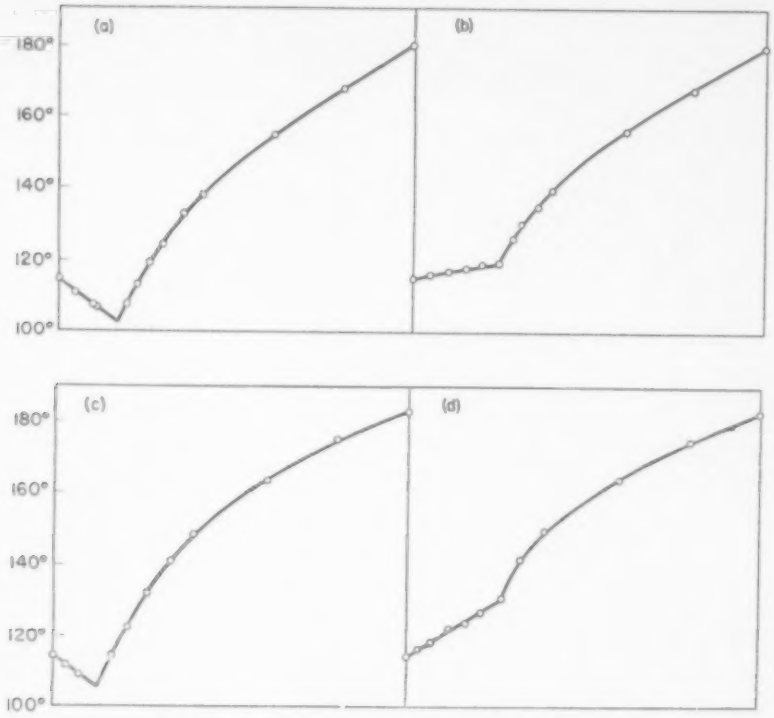


FIG. 9. (a) (+)-Methylsuccinic acid and (−)-Chlorosuccinic acid.
(b) (−)-Methylsuccinic acid and (−)-Chlorosuccinic acid.
(c) (+)-Methylsuccinic acid and (−)-Bromosuccinic acid.
(d) (−)-Methylsuccinic acid and (−)-Bromosuccinic acid.

this case is certainly due to the poor racemate-forming tendency of the halosuccinic acids.

The results of the work related above are summarized in Charts 1 and 2. The latter chart shows the configuration of the dextro-rotatory alkylsuccinic acid; as seen from the chart, most acids could be related to the others in two or more ways.

Special interest is connected with the steric relations of alkylsuccinic and alkylglutaric acids, since such acids are often obtained on oxidative degradation of natural products, e.g. terpenes. As seen from Chart 1, methylsuccinic acid could be related to malic acid and methylglutaric acid to lactic acid, in both cases by the aid of mercapto acids. Confirmation by another route was desirable, especially as (+)-methylsuccinic acid and (+)-methylglutaric acid were found to possess opposite configurations. It was therefore important that (+)-isopropylglutaric acid could be degraded to

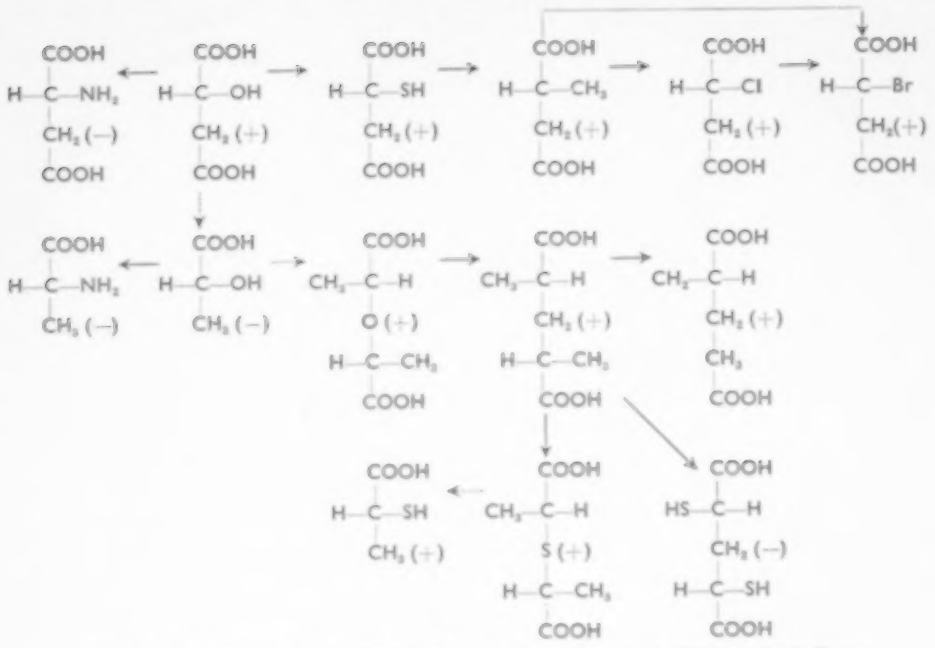


CHART 1. Fundamental correlations by the quasi-racemate method. Broken piles indicate chemical correlations by previous authors.

(−)-isopropylsuccinic acid.[34] This fact affords additional support to the conclusions regarding the methylsubstituted acids, but unfortunately the isopropylglutaric acid could not be related to the methyl derivative by the quasi-racemate method. Decisive evidence has later been produced by James,[35] who obtained both methylsubstituted acids by controlled degradation of the side chain of a steroid molecule.

A direct confirmation of the absolute configuration of the alkylsuccinic acids appeared possible by studying acids of the types:

The former are obtained by O-alkylation of malic acid and their steric relations are known. A preliminary study indicated that acids, which should possess opposite configurations give in fact quasi-racemates of rather low stability, while the acids with corresponding configurations have a certain tendency to form solid solutions, However, the examination of these systems was very tedious as the melts crystallize rather slowly and the samples were found to be very hygroscopic. The final investigation of the systems was therefore postponed; a preliminary diagram for the system O-methyl-malic acid–ethylsuccinic acid is given in Fig. 10.

In recent years, Freudenberg has determined the configuration of the alkylsuccinic acids by a purely chemical method, using the lactone of dihydroshikimic acid.[36] His results are in accordance with those found in Uppsala.

[34] A. Fredga and J. K. Miettinen, *Acta Chem. Scand.* **1**, 371 (1947).
[35] V. H. T. James, *Chem. & Ind.* 1388 (1953); *J. Chem. Soc.* 637 (1955).
[36] K. Freudenberg, *Monatsh.* **85**, 537 (1954); and quoted references.

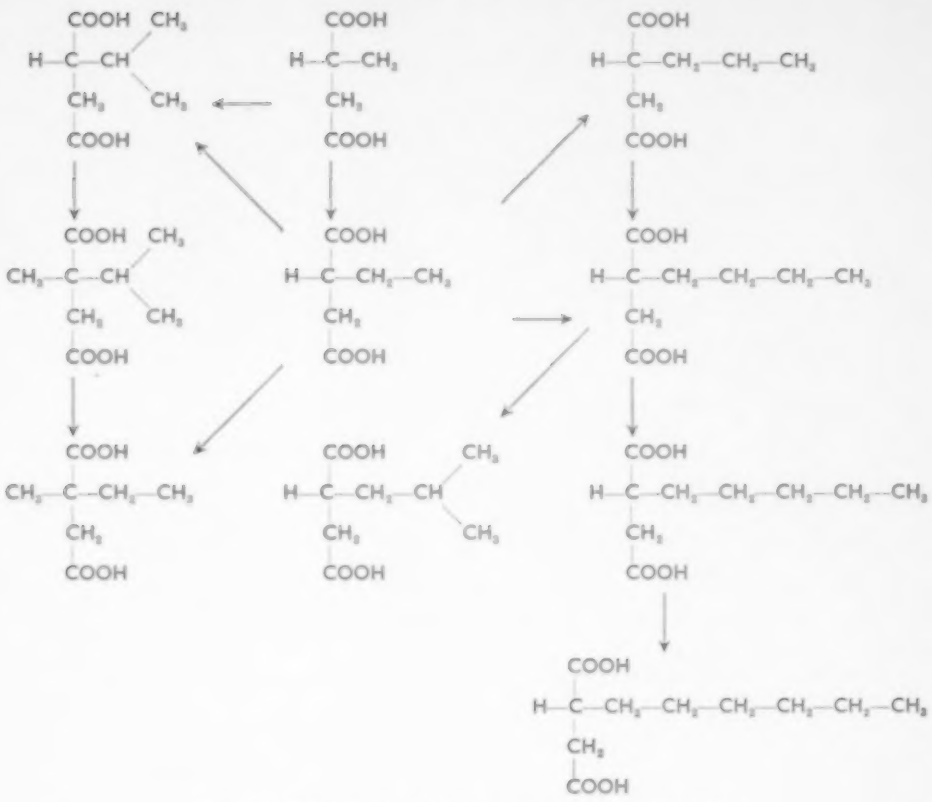


CHART 2. Configurations of dextro-rotatory alkylsuccinic acids correlated by the quasi-racemate method.

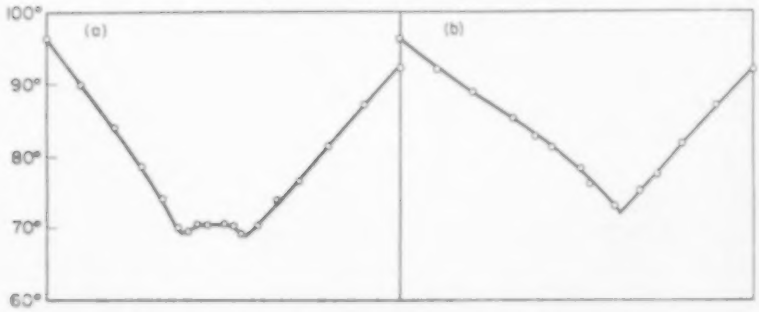


FIG. 10. (a) (−)-O-Methyl-malic acid and (+)-ethylsuccinic acid.
(b) (−)-O-Methyl-malic acid and (−)-ethylsuccinic acid.

Terpenes and related compounds

In 1941, Hückel gave a review of the steric relations inside the terpene group.[37] When the alkylsuccinic acids had been related to the glyceraldehyde system, the road

[37] W. Hückel, *J. Prakt. Chem.* [2] **157**, 225 (1941).

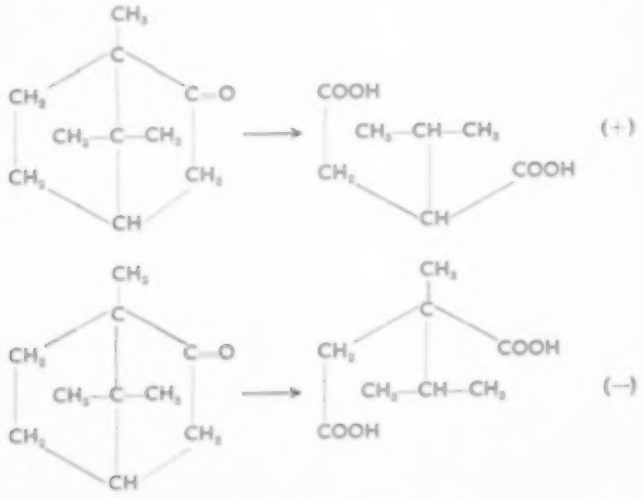
was open for connecting the terpenes to this system, and here the preparative work of previous authors could be utilized. For instance, von Braun and Jostes had connected (+)-pulegone (XVI) with (+)-methylsuccinic acid by oxidative degradation.[38] On comparison with Chart 2 we find that the methyl group of the pulegone must be situated above the plane of the paper. In another case, Henry and Paget had obtained (−)-isopropylsuccinic acid from (−)-phellandrene (XVIII).[39] Here we find that the

(+) (+) (−) (−)

XVI XVII

isopropyl group of the phellandrene must be situated above the plane of the paper.

It was also possible to connect the camphor molecule in this way. Different parts of this molecule could be connected with (+)-isopropylsuccinic acid and (−)-methylisopropylsuccinic acid as indicated below:



The first route, leading to the configuration at C_4 is rather complicated; (+)-camphor and (+)-fenchone are both related to (+)-α-pinene and the relative configurations at C_4 are known. On degradation of (+)-fenchone, Wallach obtained (−)-isopropyl-glutaric acid, which as we have seen above, is sterically related to (+)-isopropylsuccinic acid.[34,40]

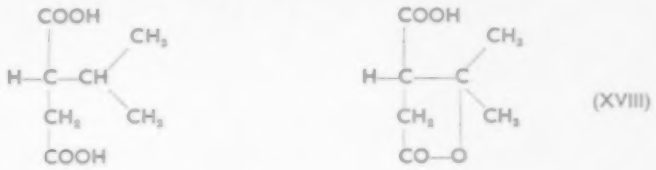
The configuration at C_1 was determined by Porath in a more direct way from camphoronic acid.[41] The two methods give consistent results: if the (+)-camphor is

[38] J. von Braun and F. Jostes, *Ber. Dtsch. Chem. Ges.* **59**, 1444 (1926).
[39] T. A. Henry and H. Paget, *J. Chem. Soc.* 70 (1928).
[40] O. Wallach, *Liebigs Ann.* **369**, 63 (1909); **379**, 182 (1911).
[41] J. Porath, *Arkiv. Kemi* **1**, 525 (1950).

written as above, the bridge must be situated behind the plane of the paper. A scheme of the absolute configurations of the principal terpenoid compounds has been given by Birch, who has also extended it to compounds of the carene group.[42]

Various natural products related to alkylsuccinic acids

Only a few examples can be given. Oxidation of (+)-isopropylsuccinic acid gives (−)-terebic acid (XVIII) of corresponding configuration.[43]



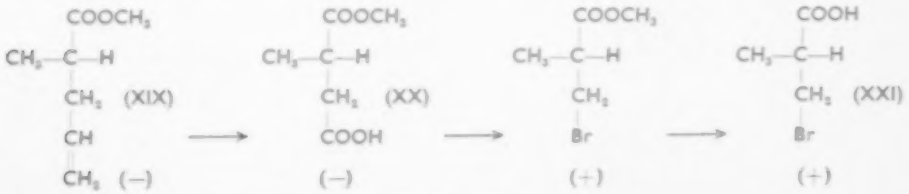
(XVIII)

By the aid of terebic acid, Crombie and Harper could establish the configuration of two cyclopropane derivatives, caronic acid and chrysanthemum acid.[44]

A small but important group of natural products is represented by isoleucine, methyl-ethylacetic acid and the anti-iso acids. These compounds were related to methylsuccinic acid by Ställberg-Stenhagen and Stenhagen.[45] They prepared (+)-methyl-allylacetic acid, which could be oxidized to (−)-methylsuccinic acid. On the other hand catalytic hydrogenation yielded (+)-methyl-propylacetic acid, which had been related to methyl-ethylacetic acid by Levene *et al.*[46] The configuration of isoleucine has later been confirmed by Trommel.[47]

Ställberg-Stenhagen has also prepared the optically active half-ester of β-methyl-glutaric acid and connected it to methyl-succinic acid.[48] The half-ester has found extensive use for synthesis of optically active long-chain compounds, e.g. tuberculo-stearic acid.[49]

Ställberg has recently found that careful oxidation of methyl methyl-allylacetate (XIX) gives a good yield of the half-ester of methylsuccinic acid (XX), which can be used for synthesis of various α-methylsubstituted acids, e.g. by Kolbe's electro-synthesis.[50] The Hunsdiecker reaction gave the ester of optically active β-bromo-isobutyric acid (XXI), which can also be used for synthetic purposes.[51]

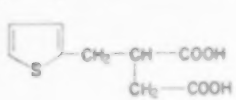


[42] A. J. Birch, *Ann. Repts. on Progress Chem.* **47**, 192 (1950).
[43] A. Fredga, *Svensk Papperstidn.* **50**, No. 11B, 91 (1947).
[44] L. Crombie and S. H. Harper, *J. Chem. Soc.* 470 (1954).
[45] S. Ställberg-Stenhagen and E. Stenhagen, *Arkiv. Kemi, Mineral. Geol.* **24B**, No. 9 (1947)
[46] P. A. Levene and R. E. Marker, *J. Biol. Chem.* **91**, 77 (1931); **98**, 1 (1932).
[47] J. Trommel, *Proc. Acad. Sci. Amst.* B **57**, 364 (1954).
[48] S. Ställberg-Stenhagen, *Arkiv. Kemi, Mineral. Geol.* **25A**, No. 10 (1947).
[49] S. Ställberg-Stenhagen, *Arkiv. Kemi, Mineral. Geol.* **26A**, No. 12 (1948).
[50] G. Ställberg, *Arkiv. Kemi* **12**, 79 (1957); **12**, 153 (1958).
[51] G. Ställberg, *Arkiv Kemi* **12**, 95 (1957).

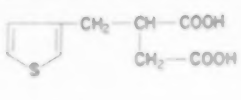
It is well-known that the methylsuccinic acid has been used for correlating steroid compounds to the glyceraldehyde system.

Thiophene derivatives

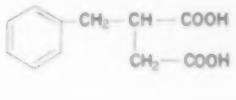
Optically active thiophene derivatives can usually be correlated to the analogous phenyl compounds. For instance, the two thenylsuccinic acids (XXII) and (XXIII) give quasi-racemates with benzylsuccinic acid (XXIV) and with each other.[52,53] In



XXII



XXIII



XXIV

this case, the three racemates and the three quasi-racemates are all isomorphous and the curves representing the quasi-racemates are of an intermediate type. An example is given in Fig. 11. Other thiophene derivatives have been investigated and connected to the phenyl compounds by Pettersson and by Gronowitz, e.g. 2- and 3-thienylsuccinic acid and the thiophene analogues of mandelic acid.[9,54,55–57]

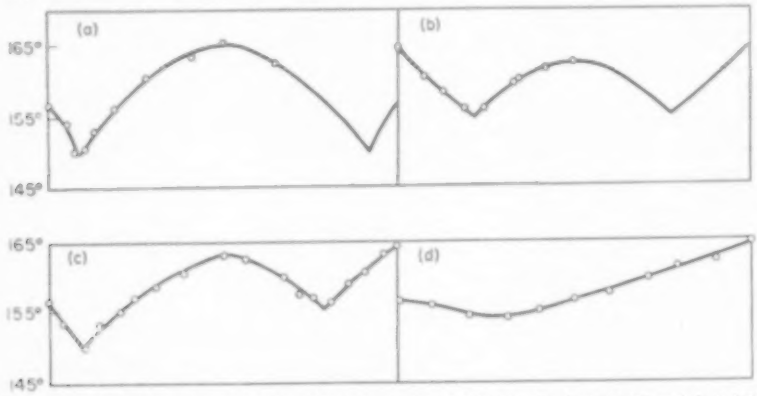


FIG. 11. (a) (+)- and (−)-XXII. (b) (+)- and (−)-XXIV. (c) (+)-XXII and (−)-XXIV. (d) (+)-XXII and (+)-XXIV.

By desulphurization with Raney nickel, the optically active thiophene derivatives can be converted into aliphatic compounds whose configuration is known previously. We have here a way to determine the absolute configuration of thiophene and benzene derivatives. Thus benzylsuccinic and phenylsuccinic acid were correlated to the alkylsuccinic acids.[58,55] The configuration of mandelic acid could be confirmed by correlation with α-hydroxycaproic acid.[57]

Synthetic plant growth regulators

The best-known natural growth regulator, indole-3-acetic acid or heteroauxin, is optically inactive and has no asymmetric carbon atom. Kögl found, however,

[52] A. Fredga and O. Palm, *Arkiv Kemi, Mineral. Geol.* **26A**, No. 26 (1949).
[53] S. Gronowitz and S. Larsson, *Arkiv. Kemi* **8**, 567 (1955).
[54] K. Pettersson, *Arkiv Kemi* **7**, 39 (1954).
[55] K. Pettersson, *Arkiv Kemi* **7**, 347 (1954).
[56] S. Gronowitz, *Arkiv Kemi* **11**, 361 (1957).
[57] S. Gronowitz, *Arkiv Kemi* **13**, 87 (1958); **13**, 231 (1958).
[58] A. Fredga, *Arkiv Kemi* **6**, 277 (1953).

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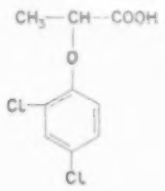
that the enantiomorphs of the next homologue, α-(indole-3) propionic acid, show an obvious difference in auxin activity.[59] Later he attributed this effect to different diffusion velocity in the plant.[60] Similar observations on optically active synthetic growth regulators were reported by several authors and now numerous compounds of this type have been studied. In some cases, the difference between the enantiomorphs is rather small, in others one form may have a very strong auxin effect while the antipode is practically inactive or even an anti-auxin. The difference may also vary considerably with the test method used, and even if differences in transport velocity may play a role in certain cases, the steric effect is certainly more complicated. It is obvious that this effect must be important for the understanding of the growth-regulating mechanism; the optically active compounds form a more subtle and more specialized instrument than the natural heteroauxin.

The synthetic growth regulators studied in Uppsala belong to three different types.

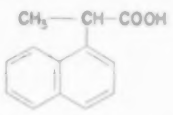
(1) α-Aryloxy-carboxylic acids, e.g. 2,4-dichlorophenoxy-propionic acid (XXV). (A certain effect is also found if the oxygen is replaced by NH, S or CH_2).

(2) α-Aryl-carboxylic acids, e.g. α-(1-naphthyl) propionic acid (XXVI). This group also includes the indole-3-propionic acid.

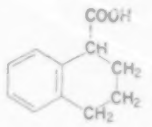
(3) Certain bicyclic acids with partially hydrated ring system, e.g. indane-3-carboxylic acid or 1,2,3,4-tetrahydro-1-naphthoic acid (XXVII).



XXV



XXVI



XXVII

In the first group, mainly investigated by Matell[61–63], the tendency to form quasi-racemates is very pronounced. All acids investigated could be correlated to one or more of the others and the possibilities of cross-checking are numerous. For instance the unsubstituted phenoxypropionic acid gives quasi-racemates with the acids having F, Cl, Br, I and CH_3 in para-position to the oxygen[10,62] and also with the 2-naphthoxy-propionic acid. The latter acid gives quasi-racemates with many other acids, among them 1-naphthoxy-, 2,4-dichlorophenoxy- and 3,4-dichlorophenoxy-propionic acid. These acids represent very interesting material for studying different types of diagrams and the decreasing stability of the quasi-racemates when the difference between the components increases. The absolute configuration was determined by the aid of the 2,4-dinitrophenoxy-propionic acid, which could be synthesized either from optically active lactic acid and 2,4-dinitrochlorobenzene or from phenoxypropionic acid by nitration. In all cases, the forms having higher auxin activity than their enantiomorphs were sterically related to D-(−)-lactic acid. The same holds good for

[59] F. Kögl, *Naturwissenschaften* **25**, 465 (1937).
[60] F. Kögl and B. Verkaaik, *Z. physiol. Chem.* **280**, 167 (1944).
[61] M. Matell, *Stereochemical Studies on Plant Growth Substances.* Thesis, Uppsala (1953). Also in *Kgl. Lantbruks-Högskis Ann.* **20**, 205 (1953); and quoted references.
[62] M. Matell, *Arkiv Kemi* **7**, 437 (1954).
[63] M. Matell, *Arkiv Kemi* **8**, 79 (1955).

the 2,4,5-trichloroanilino-propionic acid, which could be correlated to the trichlorophenoxy compound;[64] these acids form a very beautiful example of a quasi-racemate diagram (Fig. 12). It should perhaps be pointed out that arylamino acids having greater auxin effect than their enanthiomorphs are sterically related to the "unnatural" amino acids.

The acids of the second group have been studied principally by Sjöberg.[65] By the quasi-racemate method they could be correlated to each other and to the hydratropic (α-phenylpropionic) acid, whose configuration has been established by several

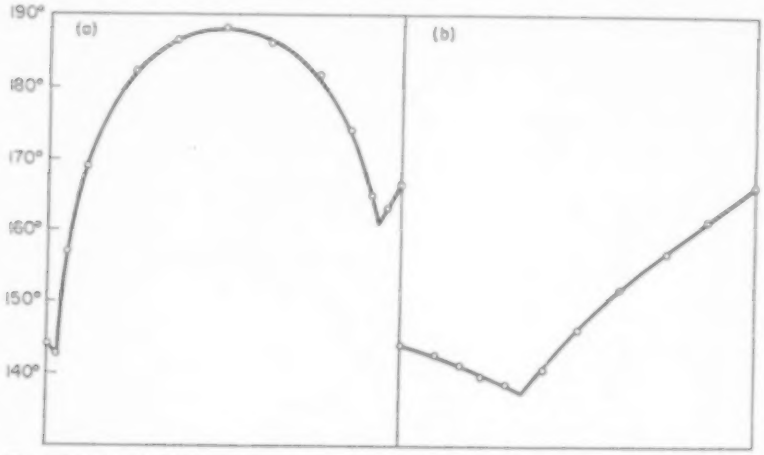


FIG. 12. (a) (−)-Trichlorophenoxy-propionic acid and (+)-trichloroanilino-propionic acid.
(b) (+)-Trichlorophenoxy-propionic acid and (+)-trichloroanilino-propionic acid.

authors (Chart 3). An example of the diagrams is given in Fig. 13: the maximum is overlapped and the curve may at first sight be mistaken for a diagram of the simple eutectic type. A more thorough investigation revealed the existence of a separate curve branch and the existence of the quasi-racemate could be confirmed by X-ray analysis.

The absolute configuration could be checked by degradation of the (+)-thionaphthenyl-2-propionic acid. On desulphurization with Raney nickel and subsequent ozonization it yielded (+)-α-methylglutaric acid. The forms having greater biological activity have analogous configuration and are all dextrorotatory (in ethanol solution). The acid XXVI forms a racemate of unusual stability, melting 80° higher than the enantiomorphs, and this acid has a central position in the chart.

Some bicyclic acids of the third group have by synthetic methods been correlated to phenylsuccinic acid.[66–69]

In the first and second group it is obvious that the higher biological effect is connected with a certain sterical configuration, and in the author's opinion conclusions as to the configuration of the antipodes of such acids can be drawn from the

[64] A. Fredga, *Arkiv Kemi* **11**, 23 (1957).
[65] B. Sjöberg, *Arkiv Kemi* **13**, 1 (1958); and quoted references.
[66] A. Fredga, *Chem. Ber.* **89**, 322 (1956).
[67] L. Westman, *Arkiv Kemi* **12**, 161 (1958).
[68] T. Mitsui, *J. Agr. Chem. Soc. Japan* **25**, 526 (1952).
[69] K. Kawazu, T. Fujita and T. Mitsui, *J. Amer. Chem. Soc.* **81**, 932 (1959).
[70] M. Matell, *Arkiv Kemi* **6**, 355 (1953).

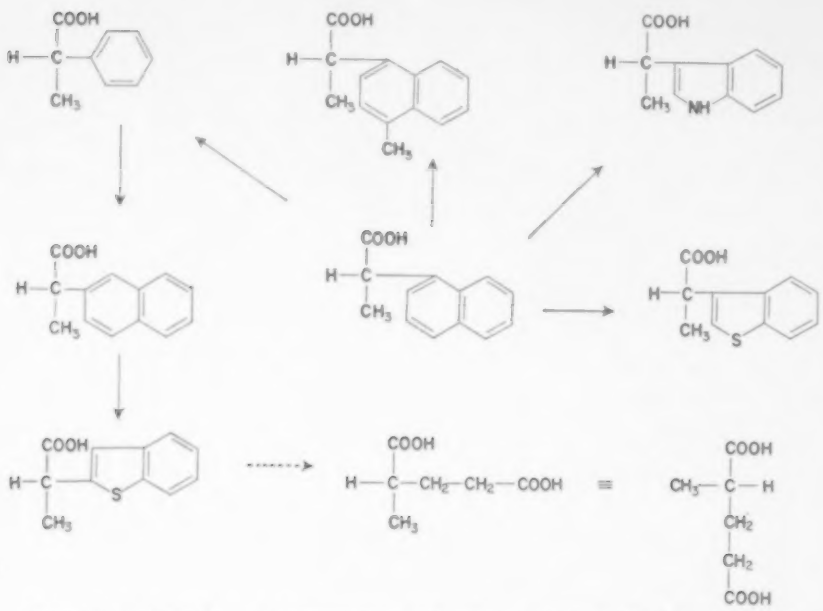


CHART 3. Configurations of dextrorotatory arylpropionic acids correlated by the quasi-racemate method. The broken pile indicates chemical correlation by degradation.

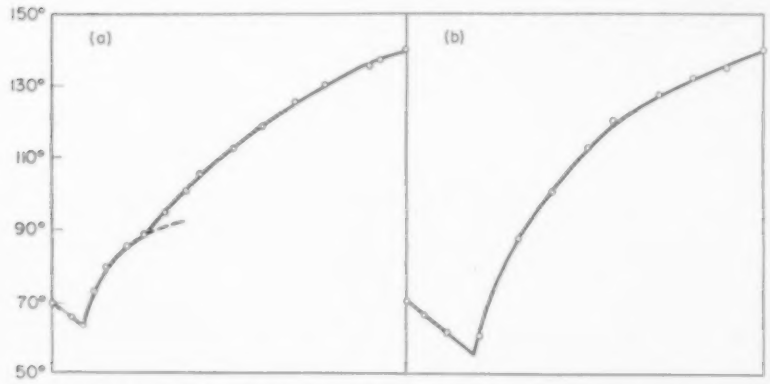


FIG. 13. (a) (−)-α-(Naphthyl-1) propionic acid (XXVI) and (+)-α-(indole-3) propionic acid. (b) (+)-α-(Naphthyl-1) propionic acid and (+)-α-(indole-3) propionic acid (B. Sjöberg).

difference in biological activity. The material of acids of the third group is still too scanty to permit any general conclusions.

As seen above, the quasi-racemate method is often used in combination with purely chemical methods, and such investigations will certainly play an important rôle in future work. Here sulphur compounds may render good service. Sulphur-containing groups are easily introduced in various molecules and afterwards the sulphur can be removed in different ways, e.g. by Raney nickel. Sulphur-containing asymmetric systems of known configuration can also be used for synthesizing larger molecules, with which sulphur-free systems may give quasi-racemates.

In the author's opinion, the quasi-racemate method is very reliable; when it gives an answer to a question of configuration, this answer is trustworthy. On the other hand, it often happens that no quasi-racemate is obtained though the possibilities may be judged as favourable. Nature keeps its secrets. It cannot be denied, that the work with this method has an element of gambling, but this makes it more thrilling and the odds are fair.

It must, however, be borne in mind that not every molecular compound between optically active substances can be regarded as a quasi-racemate. For a better understanding of the conditions for formation of racemates and quasi-racemates, a systematic investigation of the crystal structures of such compounds would be of great interest. Such studies might also throw light upon the sterical and polar factors responsible for the formation of molecular compounds and also upon the general conditions for interaction between asymmetric molecules. In this direction some work has been done, but much remains to do.

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CIS–TRANS ISOMERISM OF STEROIDAL $\Delta^{17(20)}$ ENOL ACETATES

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Natural Products Research Department, Schering Corporation, Bloomfield, New Jersey

(*Received* 18 *May* 1959)

Abstract—Structures are assigned to two pairs of geometrical isomers of steroidal $\Delta^{17(20)}$ enol acetates, based on their conversion by catalytic hydrogenation to products of known stereochemistry. The structures of 17,20-epoxides derived from one of these isomer pairs are discussed.

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ENOLIZATION of a 20-ketosteroid may be directed toward one of two positions. Depending upon conditions, either an α-hydrogen at C-21 or that on the cyclopentane ring participates, so that derived enol esters have either a terminal[1] or an exocyclic double bond. In the latter case, *cis–trans* isomerism can be envisaged, and indeed it has been possible to isolate two individual isomeric $\Delta^{17(20)}$ enol acetates in some cases. Fieser and Huang-Minlon[2] separated two enol acetates (m.p. 144–146° and 171–172°) derived from 3β-acetoxy-Δ^5-pregnen-20-one (I, Δ^5), established the fact that they were geometrical isomers around a $\Delta^{17(20)}$ double bond, but did not assign absolute structures. Marshall *et al.*[3] had also obtained a corresponding isomer pair from 3β-acetoxy-5α-pregnan-20-one (I), m.p. 121·5–122·5 and 172·5–173·5. These authors arbitrarily assigned a *trans*-structure[4] to the higher melting compound.

It seemed desirable, however, to obtain direct evidence concerning this assignment, if only to clear up the interrelationship between the enol acetates in question and certain reaction products derived therefrom. Thus, the structure of an epoxide[5] obtained from the mixture of the *cis* and *trans* enol acetates of 3β-hydroxy-5α-pregnan-20-one was considered to be the 17α, 20β-oxido-20α-acetate.[6] Assignment was made on the basis of certain steric considerations from molecular models and because of the following facts: When the epoxide in question was subjected to reduction with lithium aluminum hydride followed by acetylation, 3β,17α,20α-trihydroxy-5α-pregnane 3,20-diacetate was obtained. By analogy with a state of affairs postulated in a similar situation in ring D,[7] it was considered that this reaction involved oxide opening *without inversion* at C-20.[8] Hence the epoxide structure was proposed.

It is now possible to arrive at an assignment concerning the geometrical isomerism of the pairs of $\Delta^{17,20}$ enol acetates: When the *lower* melting isomer of Fieser's

[1] R. B. Moffett and D. I. Weisblat, *J. Amer. Chem. Soc.* **76**, 2183 (1952), H. Vanderhaege, E. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher, *Ibid.* **74**, 2810 (1952).
[2] L. F. Fieser and Huang-Minlon, *J. Amer. Chem. Soc.* **71**, 1840 (1949).
[3] C. W. Marshall, T. H. Kritchevsky, S. Liebermann, and T. F. Gallagher, *J. Amer. Chem. Soc.* **70**, 1837 (1948).
[4] C-21 bears a *trans* relationship to the quaternary C-13.
[5] T. H. Kritchevsky and T. F. Gallagher, *J. Amer. Chem. Soc.* **73**, 184 (1951).
[6] A. H. Soloway, W. J. Considine, D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **76**, 2941 (1954).
[7] N. S. Leeds, D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **76**, 2943 (1954).
[8] D. K. Fukushima and E. D. Meyer, *J. Org. Chem.* **23**, 174 (1958) exclude the intermediate formation of a C-20 ketone, since a control reduction of this same ketone gives a different yield of 20-ols than does the epoxy-acetate here discussed. However, the reaction path proposed by these authors postulates an intermediate trigonal C-20, and the sequence of events to be described below is not inconsistent with this picture. We should like to acknowledge an interesting discussion of this point with Prof. D. H. R. Barton.

$\Delta^{5,17(20)}$-pregnadiene-3β,20-diol diacetate[2] was catalytically hydrogenated to completion,[9] 5α-pregnane-3β, 20α-diol diacetate (B in Fig. 1, V in the chart) was isolated in fair yield. The same compound was obtained by an analogous hydrogenation of the *lower* melting enol acetate[3] of the Sloan–Kettering group. In both cases, therefore,

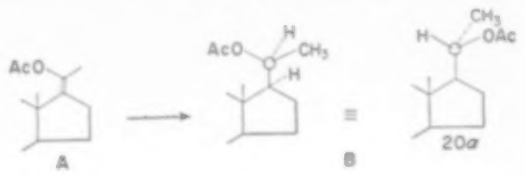

FIG. 1.

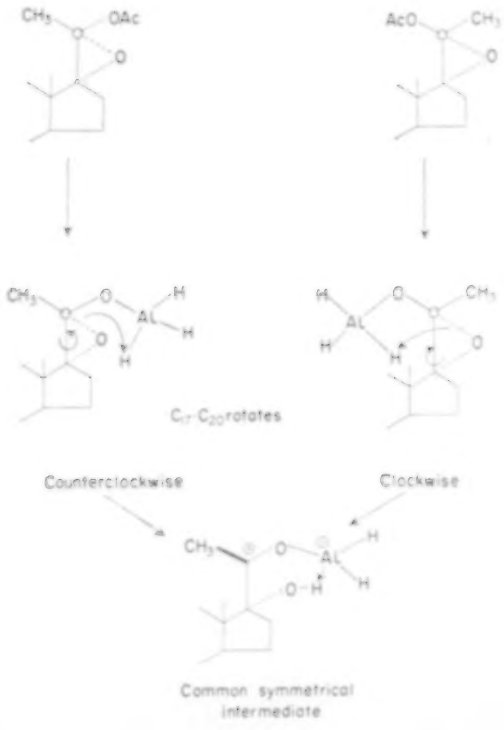

FIG. 2.

if the saturation of the enolic double bond is granted to proceed via *cis*-hydrogenation, the enol acetates in question must have the geometrical *trans* structure (A in Fig. 1, IIa in Chart 1) and, *per exclusionem*, their higher melting partners must be *cis* (IIb in the chart), accordingly.

Application of the procedures of Kritchevsky and Gallagher[5] to the individual enol acetates in the saturated series (derived from 1) resulted in the following interesting observations: When the lower melting enol acetate—now known to be the *trans*

[9] For hydrogenation of steroidal enol acetates, see R. Hirschmann, M. Brown and N. L. Wendler, *J. Amer. Chem. Soc.* **73**, 5073 (1951); J. Fajkos, *Chem. Listy*. **52**, 1320 (1958). We are indebted to Dr. Hans Reimann of these laboratories for suggesting this reaction.

isomer IIa—was subjected to the action of peracid, an oxido-acetate IIIa was obtained which differed from that obtained by the Sloan–Kettering investigators.[10] A like peroxidation of an enol acetate mixture rich in the higher melting *cis* (IIb) isomer furnished another oxido-acetate (IIIb) which appeared more similar to that recorded in the literature.[5] Reduction of the latter, followed by acetylation, furnished the known 3β,17α,20α-trihydroxy-5α-pregnane (IV) as its 3,20-diacetate, in agreement with the reported facts.[6,8] If the hydride reduction step does indeed involve an oxide opening without inversion at C-20,[6] an identical series of reactions performed on the former oxido-acetate (IIIa) possessing an epimeric situation at C-20 should produce the 3β,17α,20β-triol[11] as its 3,20-diacetate.

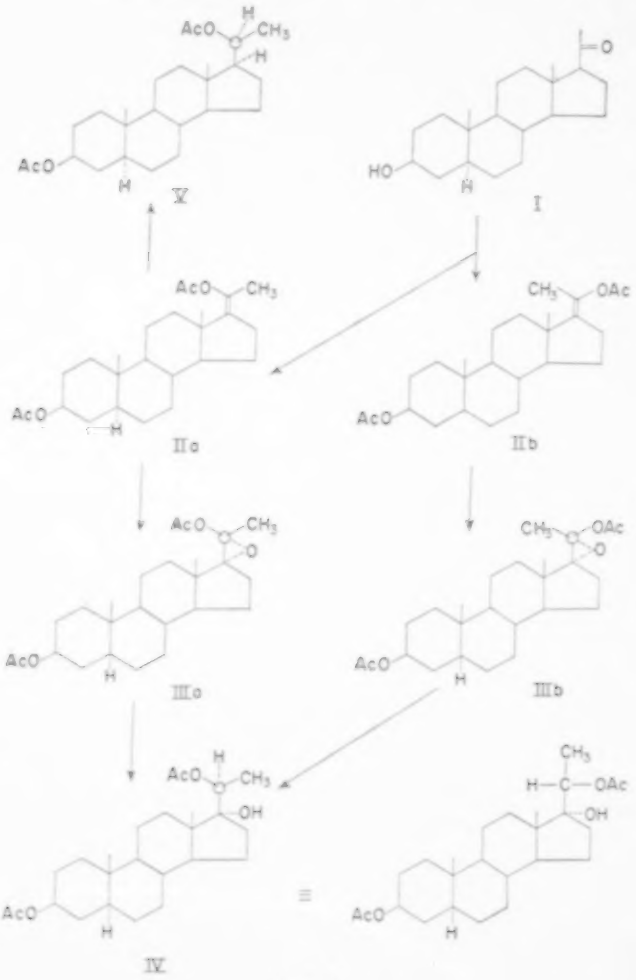

FIG. 3.

[10] We found optical rotation a more helpful criterion for characterization than melting point: the latter varies with the method of its measurement, perhaps due to thermal instability of the oxido-acetate structure.

[11] The possibility that the two oxido-acetates react via different mechanisms with lithium aluminum hydride is not considered likely.

When the experiment was carried out, however, the same 20α-ol IV was obtained as had been isolated from the C-20 isomer IIIb.

It appears thus that the course of the metal hydride reduction does not involve oxide opening without inversion at C-20, but rather that there exists a common symmetrical intermediate such as the one proposed by Fukushima and Meyer.[8] No matter from which isomeric oxido-acetate one starts, the formation of a coordination complex involving the oxygen on C-20 and the hydroxyl group at C-17 results in the existence of the common intermediate depicted in Fig. 2. The subsequent reduction occurs stereospecifically from the less hindered side opposite the angular methyl group at C-13. It follows that no argument concerning the structures of the oxido-acetates here discussed can be based on the hydride reduction. The latter follow, however, from the course of the catalytic hydrogenation.

It seems pertinent to discuss the infrared spectra of the isomeric oxido-acetates IIIa and IIIb. That of IIIb shows a single carbonyl absorption band for both its acetate groups at C-3 and at 5·76 C-20. Isomer IIIa, however, has two resolved bands, at 5·66 and 5·75. This is interpreted to be in agreement with the assigned structures since the acetyl group at C-20, being closer in space to the angular methyl group C-18 and the C-12 methylene might well be sterically strained and thus give rise to an absorption at higher frequency.

EXPERIMENTAL*

5α-Pregnane-3β, 20α-diol diacetate (V)

(a) *From* $\Delta^{5,17(20)}$ *pregnadiene-3β,20-diol diacetate* (trans). The lower melting isomer[2] from the enol acetylation reaction (IIa, Δ^5, 200 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature over palladium on charcoal (5%) 100 mg. After 4 hr, uptake had ceased (more than one equivalent of hydrogen had been taken up, suggesting some hydrogenolysis). The catalyst was removed by filtration and the filtrate concentrated to dryness. Chromatography over alumina gave a single eluate peak with benzene–petroleum ether. The central fractions (89 mg), having the highest melting points were combined and recrystallized from methanol to give 53·0 mg, m.p. 164–167°, $[\alpha]_D^{25} -0{\cdot}9$ ($CHCl_3$).[12]

(b) *From* $\Delta^{17(20)}$*-pregnene-3β,20-diol diacetate* (trans). The lower melting isomer from the enol acetylation reaction (IIa, 200 mg) was hydrogenated over 100 mg of platinum oxide and worked up as before. Product V (48 mg) was identical with that from A in melting point, rotation and infrared spectrum.

17α,20β-Oxido-5α-pregnane-3β,20α-diol diacetate (IIIa)

Lower melting enol acetate IIa[2] (200 mg) was dissolved in 15 ml ethereal perphthalic acid (39 mg/ml) and allowed to stand overnight at room temp. The solution was worked up by washing with iodide, thiosulfate, carbonate and water, drying and crystallization. From ether, 138 mg of m.p. 158–166° were obtained. Several recrystallizations from ether gave an analytical sample, m.p. 162–167°, $[\alpha]_D^{25} +14{\cdot}8°$, tetranitromethane test negative (starting material reacts to strong yellow color), λ_{max}^{Nujol} at 5·65 5·76, 8·00 and 8·16 μ. ($\lambda_{max}^{CS_2}$ at 5·66 and 5·76 μ). (Found: C, 72·10; H, 9·15, $C_{25}H_{38}O_5$ requires: C, 71·74; H, 9·15%)

17α,20α-Oxido-5α-pregnane-3β,20β-diol diacetate (IIIb)

The more polar fractions of the chromatogram from the enol acetylation of I had wide melting ranges up into the 160°s. Although not pure, they were undoubtedly rich in the *cis*-isomer IIb, and

* All melting points were taken on a Kofler Block, except where indicated, and are uncorrected. Rotations were carried out in a 1-dm. tube at a concentration of ca. 1% in the solvent specified. Analyses and spectral data were obtained by the Microanalytical and Physical Chemistry Department of the Schering Corporation.

[12] R. B. Turner and D. M. Voitle report m.p. 165–167°, $[\alpha]_D \pm 0$.

1·9 g of combined eluates were treated with perphthalic acid and worked up as before. From ether, 970 mg having m.p. 170–186° were obtained. Several recrystallizations from ether gave an analytical sample, m.p. 174–187° (a capillary m.p. was 174–176°), $[\alpha]_D^{25}$ −44·2° ($CHCl_3$)[13] λ_{max}^{Nujol} at 5·74–5·76 and 8·08 μ ($\lambda_{max}^{CS_2}$ at 5·76 μ).

(Found C, 71·92; H, 9·00. $C_{25}H_{38}O_5$ requires: C, 71·74; H, 9·15%).

5α-*Pregnane*-3β,17α,20α-*triol* 3,20-*diacetate* (IV)

Reduction of oxido-acetates IIIa and IIIb with lithium aluminum hydride and subsequent reacetylation were carried out as described by Soloway *et al.*[6]

Trans oxido-acetate IIIa (125 mg) gave a first crop of 57 mg, m.p. 245–247°, $[\alpha]_D^{25}$ −32, and a second crop of 24 mg, m.p. 241–246°. The remaining mother liquors were still crystalline and, upon paper chromatography in the heptane–methyl cellosolve system, were shown to consist of ca. 60% of the same product as the first two crops, plus ca. 30% of a slightly more polar substance—presumably the 20-epimer—plus some trace impurities.

Cis oxido-acetate IIIb (50 mg) gave 18·1 mg of the same material, m.p. 245–247°, and a second crop of 5·4 mg, m.p. 240–245°. The remaining mother liquors were shown to be largely the same material by paper chromatography; only a very small amount was attributable to the 20-epimer.

[13] The Sloan–Kettering product has m.p. 173–176°, upon recrystallization m.p. 190–193°, $[\alpha]_D^{28}$ −37° ($CHCl_3$).

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STRUCTURE MOLÉCULAIRE ET ACTIVITÉ OESTROGÈNE—XIX

PRÉPARATION STÉRÉOSÉLECTIVE DES ACIDES MÉTHYL-2(MÉTHOXY-6′-NAPHTYL-2′)-3 PENTANOÏQUES *THRÉO* ET *ERYTHRO*

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(*Received* 17 *June* 1959)

Abstract—Dehydration with formic acid of ethyl 2-methyl-3-(6′-methoxy-2′-naphtyl)-3-hydroxy-pentanoate, affords, according to the time of heating, *cis* or *trans* ethyl 2-methyl-3-(6′-methoxy 2′-naphtyl)-pent-3-en-oate. The corresponding acids, when heat decarboxylated, give selectively *cis* or *trans* 2-methyl-2-(6′-methoxy-2′-naphtyl)-pent-2-ene. Hydrogenation of these acids with Raney Nickel or Adams catalyst gives predominantly, according to the experimental conditions, *threo* or *erythro* 2-methyl-3-(6′-methoxy-2′-naphtyl)-pentanoic acids.

Résumé—La déshydratation par l'acide formique du méthyl-2(méthoxy-6′-naphtyl-2′)-3 hydroxy-3 pentanoate d'éthyle conduit, suivant la durée du chauffage, aux *cis* ou *trans* méthyl-2(méthoxy-6′naphtyl-2′)-3 pentène-3 oates d'éthyle. Les acides correspondants, décarboxylés par la chaleur, fournissent sélectivement les *cis* ou *trans* méthyl-2(méthoxy-6′naphtyl-2′)-2 pentène-2. L'hydrogénation de ces mêmes acides en présence de nickel de Raney ou de platine d'Adams conduit sélectivement, suivant les conditions expérimentales, aux acides *thréo* ou *érythro* méthyl-2(méthoxy-6′naphtyl-2′)-3 pentanoïques.

AU cours d'un premier travail d'ensemble sur la synthèse des acides de la série allénolique, l'un de nous et Horeau[1] avaient fait réagir, selon Réformatski, l'α-bromopropionate d'éthyle sur le méthoxy-6 propionyl-2 naphtalène (I) en présence de zinc et en milieu benzénique. Sans isoler les deux β-hydroxy-esters théoriquement possibles (II), le mélange réactionnel brut avait été déshydraté par le bisulfate de potassium à 200°: le mélange huileux d'esters éthyléniques obtenu avait à son tour fourni, par saponification, un mélange complexe d'acides éthyléniques à partir duquel un seul acide cristallisé (F = 166–167°) avait été isolé à l'état de pureté (avec un rendement global d'environ 26 pour cent). La fraction acide totale, non purifiée, représentait un rendement d'environ 34 pour cent. Il n'avait pas été assigné de structure à cet acide F = 166°.

Hydrogéné à l'état de sel de sodium en présence de nickel Raney, cet acide avait fourni un premier diastéréoisomère F = 128–128,5°, puis, plus laborieusement, un second, F = 109–110°.† Selon Courrier, Horeau et Jacques[2] ces deux acides possèdent des propriétés oestrogènes nettement différentes.

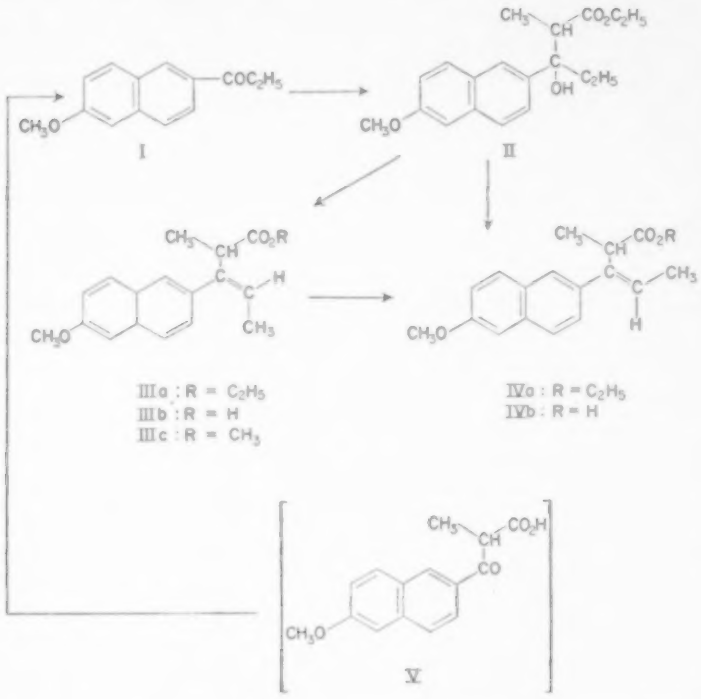
* Ce travail constitue une partie de la Thèse de Doctorat d'Université de l'un de nous (L. C. B.).

† Cette suite de réaction a été reprise quelques années plus tard par H. E. Ungnade et N. L. Jennings *J. Amer. Chem. Soc.* **73**, 873 (1951). Nous considérons qu'on ne peut tenir aucun compte des résultats décrits dans ce mémoire.

[1] J. Jacques et A. Horeau, *Bull. Soc. Chim.* 711 (1948).

[2] R. Courrier, A. Horeau et J. Jacques, *C.R. Acad. Sci., Paris* **224**, 1401 (1947).

Nous avons repris ces expériences et vérifié que cette réaction de Réformatski, que ce soit en présence de zinc ou de magnésium, fournit un mélange en proportions sensiblement identiques de deux β-hydroxy-esters diastéréoisomères que nous avons pu obtenir à l'état cristallisé (F = 85° et F = 79°).* L'un ou l'autre de ces diastéréoisomères possède, vis-à-vis des agents déshydratants, des propriétés qui les rendent indiscernables, ce qui permet d'effectuer la suite des réactions envisagées sur le mélange brut fourni par la réaction de Réformatski.



En opérant sur un de ces β-hydroxy-esters pur (F = 85°), nous avons constaté que par chauffage pendant environ 1 minute avec 5 fois son poids d'acide formique bouillant, on obtenait un mélange d'esters éthyléniques riche en un isomère cristallisant après reprise par l'eau. Cet ester très soluble dans la plupart des solvants (F = 55–56°, après recristallisation dans l'éther de pétrole) fournit par saponification l'acide F = 166°, antérieurement décrit.

Si la déshydratation formique, au lieu d'être effectuée pendant un temps très bref, est prolongée pendant 2 heures d'ébullition à reflux, le mélange d'esters éthyléniques résultant ne cristallise plus. Par saponification il fournit un mélange qui ne contient qu'un très faible proportion d'acide F = 166°, lequel peut être facilement séparé grâce à sa quasi-insolubilité dans le toluène. On peut ensuite isoler, par recristallisation fractionnée dans l'acide acétique aqueux, un nouvel acide isomère: F = 93°.

Quelques caractéristiques des deux acides et de leurs esters (les esters méthyliques ont été obtenus par action du diazométhane) sont réunies dans le Tableau 1.

* Cet aspect de la stéréochimie de la reaction de Réformatski, illustré par un certain nombre d'autres exemples, sera développé dans un mémoire qui paraîtra ultérieurement.

TABLEAU I

	Solubilité à 20° dans 100 ml		Ester éthylique	Ester méthylique
	De toluène	D'éther		
Acide F = 166° Acide F = 93°	0,15 g 17,86 g	1,03 g	F = 55–56° liquide	F = 71,5–72,5° liquide

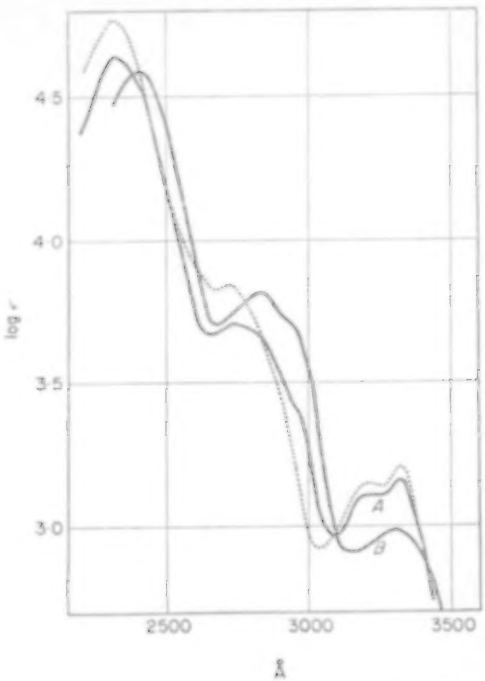


FIG. 1. Spectre d'absorption U.V. de l'acide F = 166° (trait plein) et de l'acide F = 93° (trait pointillé) (solvant: éthanol).

Les spectres ultraviolets des deux acides (Fig. 1) sont nettement différents.

Lorsque nous hydrogénons les acides F = 166° et F = 93° par le platine d'Adamsen milieu alcoolique, nous isolons très facilement, qu'il s'agisse de l'un ou l'autre des isomères, un acide saturé F = 110° qui se forme de façon nettement prépondérante. Nous retrouvons ainsi un des acides déjà décrits. Les eaux-mères de la cristallisation de cet acide, par évaporation, abandonnent un mélange.

Hydrogéné, à l'état de sel de sodium en présence de nickel de Raney, l'acide F = 166° fournit un mélange déjà obtenu par Horeau et Jacques et dont la composition, au premier abord, se montre très différente de celui que l'on obtient par hydrogénation en présence de platine. Mais, résultat inattendu, l'hydrogénation de l'acide de F = 93°, dans les mêmes conditions que son isomère, fournit en majorité et très facilement un acide F = 137° (correspondant à celui pour lequel Horeau et Jacques avaient donné un point de fusion F = 128–128,5°).

Ces premiers résultats qualitatifs nous ont incités à tenter de déterminer d'une façon plus précise, pour chaque cas, la proportion relative des diastéréoisomères formés.

Une séparation par cristallisation fractionnée ou par chromatographie ne nous paraissant pas pouvoir être suffisamment fine, et par ailleurs un dosage par spectrographie ultraviolette ou infrarouge n'étant pas possible, vu le peu de différence entre les spectres des deux isomères, nous avons eu recours à l'analyse thermique pour déterminer la composition des mélanges obtenus.

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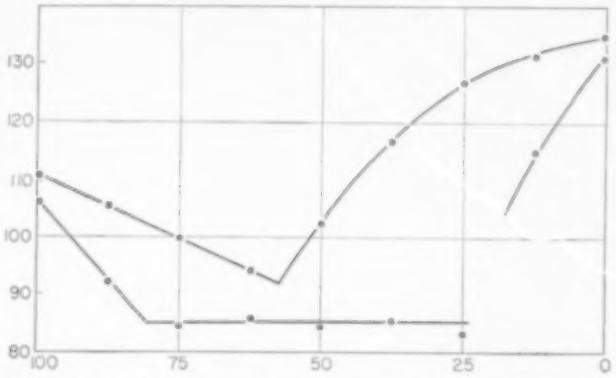


FIG. 2. Points de fusion commençante et finissante des mélanges d'acide F = 110° et d'acide F = 137°. En abcisse, les pourcentages en poids d'acide F = 110°. En ordonnées, les températures.

A partir des acides préalablement isolés nous avons établi une courbe de points de fusion des mélanges en proportions variées des deux corps purs (Fig. 2). En nous basant sur ces données nous avons pu déterminer, par la seule mesure de son point de fusion commençante et finissante, la composition du produit brut d'hydrogénation. Ces résultats des diverses expériences sont rassemblés dans le Tableau 2.

On constate que les résultats obtenus pour l'hydrogénation par le platine d'Adams en milieu acétique ou alcoolique sont pratiquement les mêmes. Lorsque les deux esters méthyliques des acides F = 166° et F = 93° sont hydrogénés par le platine d'Adams, le mélange des acides obtenu après saponification possède la même composition que dans le cas de l'acide F = 166° libre (77% de l'isomère F = 110°), mais, dans le cas de l'ester méthylique de l'acide F = 93°, l'estérification paraît augmenter la stéréosélectivité (87% de l'isomére F = 110°).

A partir des diverses observations précédentes on voit qu'il est possible, à partir du produit brut de la réaction de Réformatski, d'aboutir sélectivement à l'un ou à l'autre des acides diastéréoisomères F = 110° ou F = 137°. Pour le premier il suffit d'hydrogéner en présence du platine d'Adams le mélange des acides éthyléniques obtenu par déshydratation formique. Pour le second il convient d'hydrogéner, en présence de nickel de Raney, le mélange d'acides ethyléniques obtenu par déshydratation formique prolongée.

Ces résultats ont notablement facilité l'étude des relations stéréochimiques entre les acides bisdéhydrodoisynoliques et allénoliques menée à bien par Gay et Horeau.[3]

[3] R. Gay et A. Horeau, *Tétrahedron* **7**, 90 (1959).

TABLEAU 2

Acide soumis à l'hydrogénation	Conditions expérimentales	Pt-de fusion du mélange brut	% d'acide F = 110°	% d'acide F = 137°
F = 166°	Pt Adams 1° dans l'alcool	84–99	74	26
	2° dans l'acide acétique.	80–99	75	25
	3° ester méthylique dans l'alcool.	80–101	77	23
	Ni Raney, eau, sel de sodium	80–100	52	48
F = 93°	Pt Adams 1° dans l'alcool	84–101,5	77	23
	2° dans l'acide acétique	83–101	77	23
	3° ester méthylique dans alcool	82–104,5	87,5	12,5
	Ni Raney, eau, sel de sodium	84–124	28	72

DISCUSSION

Structure des acides éthyléniques F = 166° *et* F = 93°

Les acides précédents peuvent répondre à quatre structures possibles: il peut s'agir d'acides α,β-éthyléniques *cis* ou *trans* ou d'acides β,γ-éthyléniques *cis* ou *trans*. Mais avant de penser à résoudre le problème de leur isomérie géométrique, il importe tout d'abord de déterminer s'ils possèdent une structure d'acide α,β-éthylénique ou β,γ-éthylénique.

Nous avons trouvé que l'oxydation permanganique du sel de sodium de ces acides F = 166° ou F = 93°, en milieux aqueux, fournit un sel de céto-acide (V) qui, en solution, au voisinage de l'ébullition se décarboxyle pour donner du méthoxy-6 propionyl-2 naphtalène.

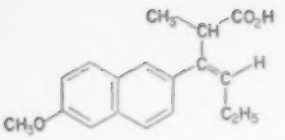
Cette suite de réactions n'est évidemment possible que si l'on est en présence d'acides β,γ-éthyléniques.

Ces résultats sont en parfait accord avec ceux que nous avons observés avec d'autres acides de la même série. A partir du méthoxy-6 butyryl-2 naphtalène et de l'α-bromopropionate d'éthyle, par une suite de réactions analogue à celle que nous décrivons, nous avons pu isoler trois acides éthyléniques isomères: VI, VII et VIII.*

Deux de ceux-ci possèdent des spectres U.V. presque superposables à ceux des acides F = 166° et F = 93° respectivement: ces deux acides, oxydés dans les mêmes conditions par le permanganate de potassium fournissent également, après décarboxylation, du méthoxy-6 propionyl-2 naphtalène, ce qui prouve qu'ils sont β,γ-éthyléniques. Le troisième acide (VIII) (qui, par élimination, doit être α,β-éthylénique) possède un spectre U.V. différent et résiste à l'oxydation permanganique dans les conditions où ses isomères sont attaqués.

La détermination de la structure *cis* ou *trans* (IIIb, IVb) de ces deux acides

* Nous reviendrons dans un prochain mémoire sur les données concernant ces acides.



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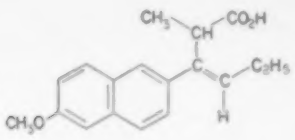

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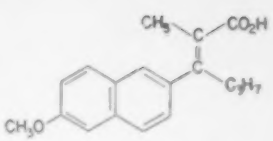
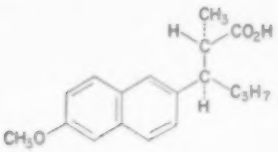


VIII



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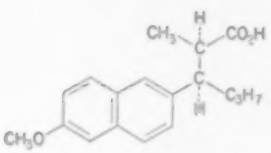

XIX

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β,γ-éthyléniques est beaucoup plus difficile: nous ne pouvons, à cet égard, que formuler des suppositions.

Un premier fait à prendre en considération concerne la stabilité relative des esters des deux acides F = 166° et F = 93° en présence d'acide formique bouillant. Nous avons vu que celui-ci permettait de transformer en grande partie l'ester de l'acide F = 166° en ester de l'acide F = 93°. D'après ces résultats on pourrait admettre que l'acide F = 166° possède la formule IIIb, où le naphtyle et le méthyle sont en *cis*, et l'acide F = 93°, plus stable, la formule IVb ou le naphtyle et le méthyle sont en *trans*, ce qui réduit les contraintes stériques entre ces deux radicaux.

Mais cette hypothèse rend évidemment mal compte de l'allure des spectres U.V. de ces deux acides; puisque l'acide F = 166° absorbe plus vers le visible et avec une intensité plus forte, ce qui devrait indiquer que la double liaison y est plus conjugée que dans son isomère plus stable. Il faut toutefois noter que l'interprétation des spectres des acides β,γ-éthyléniques de cette série est difficile, et qu'en particulier l'acide IX a un spectre pratiquement identique à celui de l'acide saturé correspondant X.

Cependant, ainsi que nous le verrons par la suite, les structures supposées permettent de rendre compte de façon assez satisfaisante des résultats de l'hydrogénation de ces deux acides.

Décarboxylation des acides β,γ-éthyléniques F = 166° *et* F = 93°

En vue d'acquérir éventuellement d'autres renseignements sur la structure de ces acides β,γ-éthyléniques F = 166° et F = 93° nous avons essayé de les décarboxyler l'un et l'autre par la chaleur.

L'acide F = 166°, chauffé vers 230° à la pression ordinaire, permet d'obtenir un composé distillant à point fixe et se présentant sous la forme d'une huile incolore, nee fournissant ni picrate, ni dérivé cristallisé avec la trinitrofluorénone.

Dans les mêmes conditions, l'acide F = 93° fournit un corps qui se prend presque totalement en masse. Débarrassé de la faible proportion d'huile qui l'imprègne, ce composé fond à 50° et donne avec la trinitrofluorénone un dérivé d'addition bien défini.

Le composé oléfinique liquide, en présence d'acide formique à chaud est isomérisé en corps F = 50°, tandis qu'il se forme simultanément dans une assez faible proportion un autre dérivé F = 167°, dont l'analyse et la détermination de sa masse

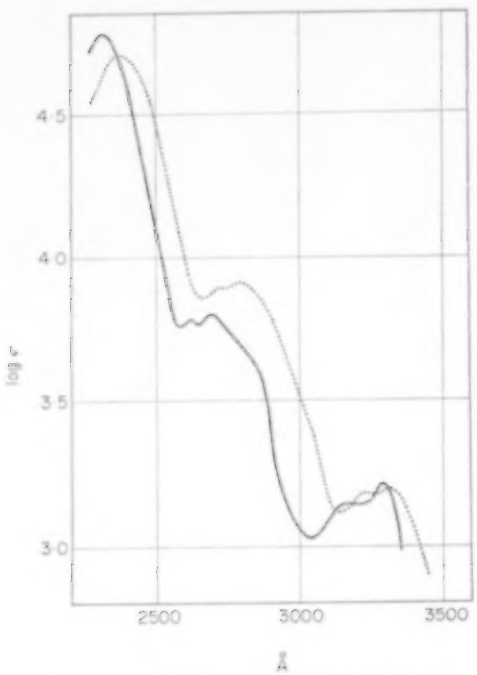
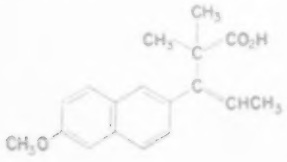


FIG. 3. Spectre d'absorption U.V. du produit XII (courbe A), du produit XIII (courbe B) et du produit XI (trait pointillé) (Solvant: éthanol).

moléculaire par cryoscopie prouve qu'il s'agit d'un dimère. L'étude de ce dernier corps a été laissée de côté. Un mélange de ce corps solide F = 50° et de son dimère se forme également très facilement lorsqu'une solution des acides F = 166° ou F = 93° dans l'acide formique est portée pendant quelque temps à l'ébullition. Les spectres de ces deux composés oléfiniques, liquide et F = 50°, sont nettement différents (Fig. 3).

En vue d'apporter des éléments de comparaison supplémentaires concernant l'interprétation de ces spectres nous avons préparé le composé XI par décarboxylation thermique de l'acide IX.

Celle-ci fournit un corps F = 21° (voir spectre U.V., Fig. 3) dont la structure a été



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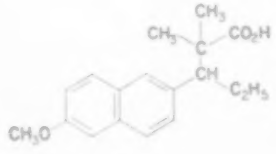

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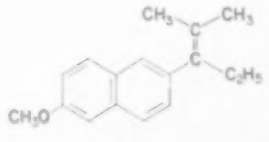

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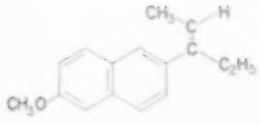

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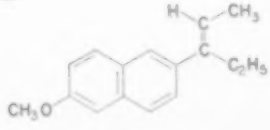


XIII

déterminée sans équivoque grâce aux résultats de son oxydation permanganique (dans l'acétone) qui fournit du méthoxy-6 propionyl-2 naphtalène.

La structure de ce dérivé oléfinique XI est d'ailleurs conforme à celle que prévoit le mécanisme de la décarboxylation thermique des acides α,β ou β,γ-éthyléniques proposé par Arnold, Elmer et Dodson,[4] mécanisme qui fait intervenir un état de transition cyclique avec déplacement de la double liaison que nous constatons effectivement par rapport à l'acide IX.

Nous proposons pour le composé liquide la structure XII et la structure XIII pour le corps F = 50° à partir des considérations suivantes:

(1°) Le composé éthylénique F = 50°, le plus stable, possède en effet la structure où les interactions entre le méthyle et le naphtyle sont moindres.

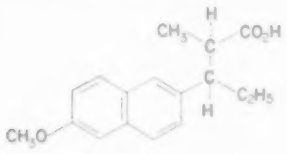
(2°) La ressemblance entre les spectres des corps XII et IX est nette: dans les deux cas il y a interactions entre le noyau naphtalénique et le méthyl *cis*.

Cram et Abd Elhafez[5] ont attribué les structures du *cis* α-méthylstilbène (F = 48°) et du *trans* α-méthylstilbène (F = 81–82°) sur la base de considérations semblables. Le carbure *trans* absorbe plus vers le visible avec une intensité plus grande que son isomère. Antérieurement Ellingboe et Fuson[6] avaient montré que le carbure F = 48° est isomérisé en F = 81° par traitement acide.

Il nous est impossible actuellement, considérant comme démontrée la structure β,γ-éthylénique des acides F = 166° et 93°, de fournir une explication à la stéréosélectivité de leur décarboxylation thermique.

Hydrogénation stéréosélective des acides β,γ-éthyléniques F = 166° *et* F = 93°

Une explication rigoureuse du mécanisme de l'hydrogénation stéréosélective des acides F = 166° et F = 93° suppose remplies deux conditions préalables: la connaissance définitive des structures des acides de départ et celle des acides saturés diastéréoisomères *thréo* (XIV) et *érythro* (XV) auxquels ils donnent naissance. Ce n'est malheureusement pas le cas.



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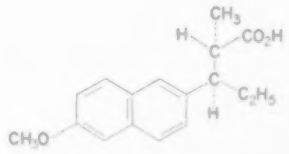
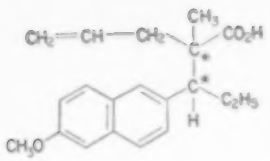


XV

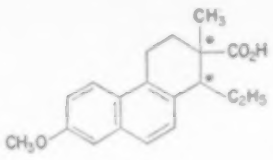
Le problème de la détermination de la structure des acides saturés F = 137° et F = 110° est en effet particulièrement difficile. Nous ne pouvons penser le résoudre par des preuves chimiques; nos conclusions ne pourront être qu'étayées par un ensemble de recoupements indirects.

Gay[7] a pu démontrer, sur un cas particulier, la configuration des diastéréoisomères répondant à la formule XVI en réalisant le passage de ces dérivés allénoliques aux acides bisdéhydrodoisynoliques (XVIII) *iso* et *normal*, pour lesquels la position *cis* et

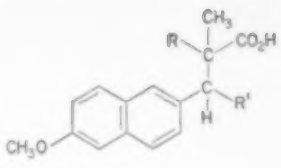
[4] R. T. Arnold, Elmer et R. M. Dodson, *J. Amer. Chem. Soc.* **72**, 4359 (1950).
[5] J. Cram et F. A. Abd. Elhafez, *J. Amer. Chem. Soc.* **74**, 5829 (1952).
[6] E. Ellingboe et R. C. Fuson, *J. Amer. Chem. Soc.* **55**, 2964 (1933).
[7] R. Gay, *C.R. Acad. Sci., Paris* **242**, 3084 (1956).



XVI



XVII



XVIII

R > CH_3 ; R' = C_2H_5 or C_3H_7

trans des groupements éthyle et carboxyle a été démontrée par Miescher et ses collaborateurs.[8]

De l'ensemble des résultats de Gay on peut tirer plusieurs conclusions concernant la configuration des acides répondant à la formule générale XVIII.

1°. Considérant comme démontrée la configuration de l'acide XVI (et des produits qui en dérivent par hydrogénation de la chaîne allylique), on note que les esters correspondants aux acides possédant une structure *érythro* sont, au cours de la chromatographie sur alumine, moins retenus que leurs isomères *thréo*. On peut, dans une première hypothèse, généraliser cette observation à tous les esters des acides de formule XVIII et supposer que tous les composés les moins retenus ont la même configuration *érythro*.

2°. Cette première supposition se trouve renforcée par le fait que tous les esters les moins adsorbés sur alumine correspondent aux acides qui ont les propriétés oestrogènes les plus marquées.[9]

A partir de ces remarques et en supposant qu'il est légitime d'en étendre la validité aux acides qui nous intéressent, nous pouvons admettre que l'acide F = 137° obtenu en présence de nickel de Raney à la configuration *érythro* (XV) tandis que l'hydrogénation en présence de platine des deux acides éthyléniques fournit préférentiellement l'isomère *thréo* (F = 110°) XIV.*

En effet comme dans tous les couples examinés par Horeau, Gay et Courrier[9] l'acide F = 137°, le plus oestrogène est, sur alumine, moins retenu que son isomère F = 110°.

Il existe enfin un autre argument en faveur de la configuration *thréo* de l'acide F = 109°.

L'acide VIII (voir p. 154), dont nous savons qu'il est α,β-éthylénique, et qui possède vraisemblablement une configuration où le carboxyle et le méthoxynaphtyle sont *trans*, fournit par hydrogénation, un acide F = 117°. D'après ce que l'on sait de l'hydrogénation catalytique des oléfines *cis* et *trans*,[10] on peut admettre que le corps formé en prépondérance doit avoir la configuration *thréo* (XIX). Ce même acide F = 117° est obtenu par hydrogénation des acides VI et VII en présence de platine d'Adams. Or l'hydrogénation en présence de nickel de Raney du sel de sodium de

* Pour les acides de formule générale XVIII, on a nommé *érythro*, conformément à la définition classique, les corps dont la configuration est telle que dans une conformation possible les substituants éclipsés présentent une certaine analogie. Le terme *thréo* désignant l'autre isomère. Les substituants qui se correspondent étaient classés par ordre de "grosseur" $CO_2H > R > CH_3$ (sur le carbone α) et $(CH_3O)\ C_{10}H_6 > R > H$ sur le carbone β. Dans le cas des acides F = 137° et F = 110°, selon le même principe, nous avons $CO_2H > CH_3 > H$ (sur le carbone α) et $(CH_3O)\ C_{10}H_6 > C_2H_5 > H$ sur le carbone β.

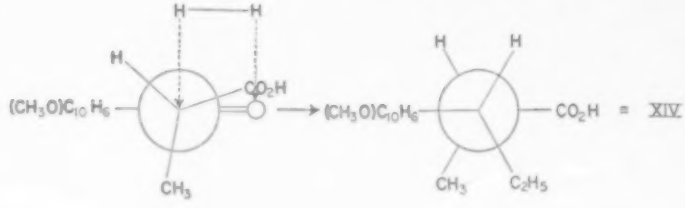
[8] K. Miescher, *Chem. Rev.* **43**, 367 (1948).
[9] A. Horeau, R. Gay et R. Courrier, *C.R. Acad. Sci., Paris* **242**, 429 (1956).
[10] R. L. Burwell, *Chem. Rev.* **57**, 895 (1957).

l'acide VIII, dont le spectre U.V. est presque superposable à celui de l'acide F = 93° (IVa) fournit un autre acide F = 145°, que nous considérons comme *érythro* (XX) et qui effectivement est plus oestrogène et moins retenu sur alumine que son isomère F = 117°.

Quoiqu'il en soit, ces conclusions, dont nous reconnaisons qu'elles ne représentent qu'un ensemble de probabilités, serviront de bases aux considérations qui suivent.

Si nous retenons pour l'acide F = 166° la formule IIIb et pour l'acide F = 93° la formule IVb, nous allons voir que celles-ci permettent également de proposer une explication cohérente des résultats de leur hydrogénation.

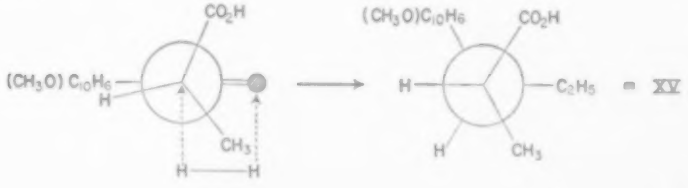
Si l'acide éthylénique F = 166° à une conformation telle que XXI, on conçoit que l'hydrogène saturant la double liaison éthylénique arrive par le côté le moins encombré de la molécule et fournisse, en présence de platine, l'isomère *thréo* (XIV).



XXI = XIV

Le fait qu'en présence de nickel de Raney le sel de sodium de l'acide insaturé F = 166° conduise à des résultats d'hydrogénation moins sélectifs peut s'expliquer par l'isomérisation (catalysée par le nickel) de cet acide F = 166° en acide F = 93°. L'expérience vérifie d'ailleurs cette supposition. Alors que le sel de sodium de l'acide F = 166°, hydrogéné par le nickel de Raney, fournit 52 pour cent d'isomère *thréo*, lorsque ce même sel est agité à l'air avec le catalyseur pendant une heure avant de l'être en atmosphère d'hydrogène la proportion d'acide *thréo* tombe à 35 pour cent, c'est-à-dire que la composition du mélange obtenu se rapproche nettement de celui (riche en *érythro*) qui résulte de l'hydrogénation de l'acide F = 93°.

En ce qui concerne les résultats de l'hydrogénation de l'acide β,γ-éthylénique F = 93°, on peut admettre, pour ce dernier, une conformation correspondant au schéma XXII:



XXII = XV

Ici la tendance de l'hydrogène à éclipser le naphtyle sera d'autant plus grande que la salification de la fonction acide fournira un ion qu'une solvatation vraisemblable grossira sensiblement. L'hydrogène arrivant cette fois également par le côté le moins encombré de la molécule, le produit saturé obtenu en majorité sera alors l'isomère *érythro* (XV).

Pour rendre compte la formation d'isomère *thréo* par l'hydrogénation de l'acide F = 93° en milieu acétique et en présence de platine, il faut admettre qu'une conformation très voisine de XXI est également possible: les modèles moléculaires montrent que cette conformation n'est pas incompatible avec l'encombrement des groupes présents.

PARTIE EXPERIMENTALE

Sauf indication spéciale, les points de fusion sont mesurés au bloc Maquenne, et non corrigés.

Méthyl-2(méthoxy-6'naphtyl-2')-3 hydroxy-3 pentanoate d'éthyle (II)

On opère exactement suivant le protocole antérieurement décrit:[a] 50,6 g de propionyl-2 méthoxy-6 naphtalène, 43 g d'α-bromopropionate d'éthyle, 15,6 g de zinc en planures dans 570 ml de benzène sont chauffés 1 hr 30 min à reflux. A près refroidissement le produit de la réaction est hydrolysé par une solution d'acide sulfurique à 10%. On lave à l'eau la couche benzénique, sèche sur SO_4Na_2 et évapore le solvant. On obtient 70,7 g de produit brut totalement pris en masse.

20 g du produit brut précédent sont dissous à chaud dans 100 ml d'hexane. Il cristallise par refroidissement 9,05 g de fines aiguilles F = 83–84°. On recristallise une seconde fois dans l'hexane; F = 85–86°*.

Analyse—$C_{18}H_{24}O_4$. Calc. %: C = 72,1; H = 7,65;
Tr. C = 72,0; H = 7,8.

Méthyl-2 (méthoxy-6'naphtyl-2')-3 pentène-3 oate d'éthyle (IIIa)

On porte à ébullition une minute, 10 g de méthyl-2(méthoxy-6 naphtyl-2)-3 hydroxy-3 pentanoate d'éthyle (F = 81,5–83,5°) dans 50 ml d'acide formique. On jette le tout dans de l'eau, extrait à l'éther. L'extrait éthéré est neutralisé par une solution de bicarbonate de sodium à 5%, lavé avec de l'eau, séché sur sulfate de sodium anhydre et distillé. On obtient 9,7 g d'esters éthyléniques qui cristallisent partiellement.

Une fraction de cet ester (1,1 g) a été recristallisée dans 3 ml d'éther de pétrole (E = 35–50°); après trois recristallisation, on obtient de fines aiguilles F = 55–56°.

Analyse—$C_{18}H_{22}O_3$. Calc. %: C = 76,5; H = 7,4;
Tr. = 76,5; H = 7,3.

Acide méthyl-2(méthoxy-6'naphtyl-2')-3 pentène-3 oïque (IIIb)

On saponifie directement en chauffant à reflux les 9,7 g d'ester brut précédent avec 10 ml de soude 10 N et 60 ml de méthanol pendant 30 minutes. On reprend largement par l'eau et extrait l'insaponifiable à l'éther. La solution aqueuse alcaline est acidifiée par l'acide acétique; une huile précipite et cristallise. On essore, recristallise le produit bien sec dans 50 ml de toluène et obtient 2,430 g, d'acide $F_{inst.}$ = 161–162° qu'on recristallise dans le toluène, puis sèche sous vide pour analyse: $F_{inst.}$ = 166–167°.

Analyse—$C_{17}H_{18}O_3$. Calc. %: C = 75,5; H = 6,7;
Tr. C = 75,1; H = 6,8.

Les eaux-mères sont évaporées à sec. Le résidu recristallisé dans l'acide acétique aqueux fournit 1,450 g. d'acide F = 93–94°.

Méthyl-2(méthoxy-6' naphtyl-2')-3 pentène-3 oate de méthyle (IIIc)

2 g d'acide F = 166° sont traités par une solution éthérée de diazométhane. La réaction est très lente et nécessite une agitation de temps en temps. Après les traitements habituels on récolte quantitativement l'ester qui est recristallisé dans 25 ml de méthanol + 5 ml d'eau. Rdt. 1,72 g, F = 71,5–72,5°. Belles aiguilles feutrées.

Analyse—$C_{18}H_{20}O_3$. Calc. %: C = 76,0; H = 7,1;
Tr. C = 76,1; H = 7,0

* La séparation de l'autre isomère F = 79° et l'étude plus complète de cette réaction de Réformatski feront l'objet d'un autre mémoire.

Acide méthyl-2(méthoxy-6′ naphtyl-2′)-3 pentène-3 oïque (IVb)

On chauffe 39,65 g de méthyl-2(méthoxy-6 naphtyl-2)-3 hydroxy-3 pentanoate d'éthyle brut de la réaction de Réformatski avec 160 ml d'acide formique pendant 2 heures. On distille l'acide formique au bain-marie sous vide et obtient 36 g, 45 d'ester éthylénique liquide que l'on saponifie directement.

On chauffe à reflux ces 36, 45 g d'ester éthylénique avec 40 ml de soude 10 N et 360 ml de méthanol pendant 2 heures. On distille le méthanol, étend d'eau et extrait l'insaponifiable à l'éther. La solution aqueuse alcaline est acidifiée par l'acide acétique et donne une huile qui cristallise. On essore 26 g d'acide. Le tout, recristallisé au toluène, donne 3,72 g d'acide F = 161–162°.

Les eaux-mères sont évaporées à sec. Le résidu recristallisé dans l'acide acétique aqueux fournit 7,95 g d'acide F = 93,5–95°. On recristallise une seconde fois pour analyse.

Analyse—$C_{17}H_{16}O_3$. Calc. %: C = 75,5; H = 6,7;
Tr. C = 75,5; H = 6,7

Les esters méthylique et éthylique de cet acide ne sont pas cristallisés.

Oxydation permanganique des acides F = 166° *et* F = 93°

On transforme 0,100 g d'acide F = 166° en sel de sodium avec une quantité suffisante de soude 0,1 N jusqu'à franche alcalinité en présence d'un cristal de phénol phtaléine. On dilue la solution avec 10 ml d'eau distillée, puis refroidit avec de la glace fondante. A la solution agitée magnétiquement on ajoute goutte à goutte 1,74 ml de solution de permanganate à 4,72% dilué dans 10 ml d'eau (l'addition dure environ 5 minutes). Après l'addition, on agite encore 5 minutes et essore le précipité de bioxyde de manganèse. La liqueur limpide est portée à l'ébullition pendant 10 minutes. Un peu avant le début de l'ébullition un trouble apparaît qui s'organise rapidement. On l'extrait avec 50 ml d'éther. L'extrait éthéré est lavé à l'eau, séché sur sulfate de sodium et évaporé. On obtient 0,037 g de cristaux blancs, F = 100–102° brut. Le point de fusion mélangé avec le propionyl-2 méthoxy-6 naphtalène n'accuse aucune dépression.

La solution alcaline, acidifiée par l'acide acétique, redonne un peu d'acide de départ n'ayant pas réagi.

En opérant de la même façon et sur des quantités identiques d'acide F = 93°, on obtient le méthoxy-6 propionyl-2 naphtalène avec le même rendement.

Décarboxylation thermique de l'acide diméthyl-2,2(méthoxy-6′naphtyl-2′)-3 pentène-3 oïque (IX): *méthyl-2(méthoxy-6′ naphtyl-2′)-3 pentène-2* (XII)

15 g d'acide diméthyl-2,2 (méthoxy-6′naphtyl-2′)-3 pentène-3-oïque dans un ballon à distiller sont chauffés au bain métallique entre 230° (commencement du départ de CO_2) et 280°. L'opération dure environ 30 minutes. Le carbure obtenu est directement distillé sous vide E_{12} = 186–187°. n_D^{20} = 1,5942; Rt—11,75 g. Cette huile se prend en masse. F = 21°. (Spectre U.V. voir Fig. 3).

Analyse—$C_{17}H_{20}O$. Calc. %: C = 84,95; H = 8,4:
Tr. C = 84,45; H = 8,2.

Oxydation permanganique du méthyl-2(méthoxy-6′ naphtyl-2′)-3 pentène-2

1 g de carbure précédent, 1 g de permanganate de potassium finement pulvérisé et 30 ml d'acétone sont agités pendant 3 jours à la température ordinaire. Après filtration de l'oxyde de manganèse et évaporation du solvant le résidu huileux est recristallisé dans le méthanol: on récolte facilement 170 mg de méthoxy-6 propionyl-2 naphtalène F = 110° (pas d'abaissement avec un échantillon authentique).

Décarboxylation thermique des acides méthyl-2(méthoxy-6′ naphtyl-2′)-3 pentène-3 oïques: (méthoxy-6′ naphtyl-2′)-3 pentène-2 cis et trans. (XII et XIII)

(1°) *Acide* F = 166°. Dans un appareil à distiller, 2 g d'acide F:166° sont chauffés progressivement au bain métallique vers 240° jusqu'à cessation de dégagement du gaz carbonique. On laisse refroidir le bain jusqu'à 220° et distille sous vide le carbure formé; on obtient 1,13 g de carbure incolore. Celui-ci est dissout dans l'éther, lavé à la soude 0,5 N, puis à l'eau; on sèche sur sulfate de sodium et distille de nouveau sous vide: E_{20} = 192,5–195,5°. n_D^{23} = 1,6020 (Spectre U.V. voir Fig. 3).

Analyse—$C_{16}H_{18}O$. Calc %: C = 84,9; H = 8,0;
Tr. C = 85,1; H = 8,1.

(2°) *Acide* F = 93°. On opère comme précédemment, et obtient un carbure avec un rendement identique (E_{20} = 197–200°) qui se prend presque totalement en masse. Débarrassé sur plaque poreuse de l'huile qui l'imprègne, ce carbure se présente en écailles incolores F = 49–51° (petit tube) (Spectre U.V., voir Fig. 3).

Analyse—$C_{16}H_{18}O$. Calc. %: C = 84,9; H = 8,0;
Tr. C = 84,45; H = 8,1.

Contrairement à son isomère liquide ce carbure cristallisé, traité dans les conditions habituelles par trinitrofluorénone fournit un composé d'addition rouge brique. Fines aiguilles, $F_{inst.}$ = 113°.

Analyse—$C_{16}H_{18}O + C_{13}H_5N_3O_7 = C_{29}H_{23}N_3O_8$
Calc. %: C = 64,3; H = 4,3;
Tr. C = 64,25; H = 4,5.

Décarboxylation par l'acide formique de l'acide F = 166°

2 g d'acide dans 20 ml d'acide formique anhydre sont portés à l'ébullition deux heures. Après reprise par l'eau et l'éther, la phase éthérée est lavée à l'eau, puis à la soude diluée (ce qui permet de récupérer 0,32 g d'acide initial F = 155–162°). La phase neutre, après évaporation de l'éther pèse 1,4 g. Par reprise de cette fraction par 20 ml de méthanol on récolte 0,25 g d'une poudre incolore, insoluble, même à chaud F = 163–165°. Par évaporation des eaux-mères on obtient 1,1 g d'huile qui est dissoute dans 17 ml de méthanol +0,5 ml d'eau. Après décantation d'une huile résineuse très colorée, puis évaporation lente on obtient le carbure précédent F = 49–50°.

La fraction insoluble est recristallisée dans le méthoxy-éthanol (ou l'acide acétique) F = 167–168°.

Analyse—C_1-$H_{18}O$. Calc. %: C = 84,9; H = 8,0;
Tr. C = 84,8; H = 8,0.

Masse moléculaire par cryoscopie dans le camphre: trouvée 436,418; calculée pour $C_{16}H_{18}O \times 2$ = 452.

Hydrogénation des acides méthyl-2(méthoxy-6' naphtyl-2')-3 pentène-3 oïques

(a) *Hydrogénation de l'acide* F = 93° *dans l'alcool en présence de platine Adams.* On hydrogène 1,35 g d'acide F = 92° dans 15 ml d'alcool en présence de 0,200 g de platine Adams. En 24 minutes, 157 ml d'hydrogène sont absorbés. On essore le platine, précipite les acides saturés par addition d'une quantité suffisante d'eau et obtient 1,020 g d'acide F = 98–99°. Par recristallisation dans l'éthanol aqueux on récolte 0,820 g d'acide F = 108,5–110° déjà décrit par Jacques et Horeau.[2]

(b) *Hydrogénation de l'acide* F = 166° *dans les mêmes conditions.* Après 32 minutes 162 ml d'hydrogène sont absorbés. On essore le platine, précipite les acides saturés par addition d'une quantité suffisante d'eau et obtient 0,920 g d'acide. Le tout recristallisé dans l'éthanol aqueux donne 0,030 g d'acide F = 121–131° (mélange) et 0,810 g d'acide F = 108–110°.

(c) *Hydrogénation de l'acide* F = 93° *en présence de nickel de Raney.* On dissout 1,35 g, d'acide F = 93° dans 5 ml de soude N, ajoute 4 g de Ni (préparés à partir de 12 g d'alliage de Raney) et 35 ml d'eau distillée. Au bout de 29 minutes, 117 ml d'hydrogène sont absorbés (théorie 120 ml). On filtre et rince le nickel abondamment à l'eau. La liqueur aqueuse est acidifiée par de l'acide acétique. On extrait l'acide formé à l'éther, lave la solution éthérée à l'acide chlorhydrique N, puis à l'eau, sèche sur sulfate de sodium anhydre et évapore. On récolte 1,350 g, de produit. Par recristallisation dans l'éthanol aqueux on obtient 0,880 g, d'acide en cristaux fins F = 132–134°. Une seconde cristallisation élève le point de fusion à 136,5–137,5°. (Jacques et Horeau[2] indiquent F = 128–128,5°).

(d) *Hydrogénation de l'acide* F = 166° *dans les mêmes conditions.* Au bout de 30 minutes l'hydrogénation s'arrête d'elle-même, 76 ml d'hydrogène sont absorbés. On opère ensuite comme précédemment et obtient 1,35 g, de mélange des deux acides saturés F = 109–110° et F = 136,5–137,5°.

Diagrammes thermiques des mélanges d'acides F = 109° *et* F = 136°

On prépare deux solutions 0,05 g de chaque acide dans 20 ml de benzène anhydre. On les mélange en proportions variables de façon a avoir à chaque fois 3 à 4 ml de solution de titre connu; on mesure après évaporation totale, les points de fusion commençante et finissante au bloc de Köfler, sous microscope (voir Fig. 2). Quand il règne une incertitude sur la composition d'un échantillon inconnu (un mélange contenant 50% de chaque composant fond comme un mélange constitué par 87,5% d'isomère F = 110° et 12,5% d'isomère F = 137°), il suffit d'ajouter une certaine quantité de l'un ou de l'autre des acides pour savoir sur quel segment de la courbe on se trouve.

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SYNTHETIC INVESTIGATION ON THE BUILDING OF RING A OF STEROIDS

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Abstract—Methyl 7-keto-1,2,3,4,4a,5,6,7-octahydronaphthoate (Va) has been prepared by the reduction of 7-methoxy-1,2,3,4-tetrahydronaphthoic acid (III) with lithium and ammonia followed by hydrolysis of the enol ether, esterification and migration of the double bond. Alkylation of Va has led to the substitution at the expected 8-position. Methyl 4-keto-7-methoxy-1,2,3,4-tetrahydronaphthoate (X), an intermediate in the preparation of III, has been converted into methyl 3-methyl-3-cyano-4-keto-7-methoxy-1,2,3,4-tetrahydronaphthoate (XIII).

FOR the attachment of ring A to the tricyclic intermediates in the B, C, D route for the synthesis of steroids, it has often been found expedient to protect the more reactive methylene group adjacent to the carbonyl function by a methylanilinomethylene group.[1] Model experiments using a suitably substituted bicyclic ring system, for the development of a new method dispensing with the necessity of a protecting group, have been described in the present communication.

It has been established that 3-methyl-4-ethoxycarbonylcyclohex-2-ene-1-one (I, Hagemann ester) is exclusively alkylated at the 2-position[2] in the absence of a protecting group on the keto methylene. The essential feature of this compound is the presence of a vinylogous β-keto ester function which facilitates the formation of the carbanion (II) in the presence of a base. It appeared to us that a decalin derivative, such as Va, carrying the Hagemann ester system distributed in its two rings would be

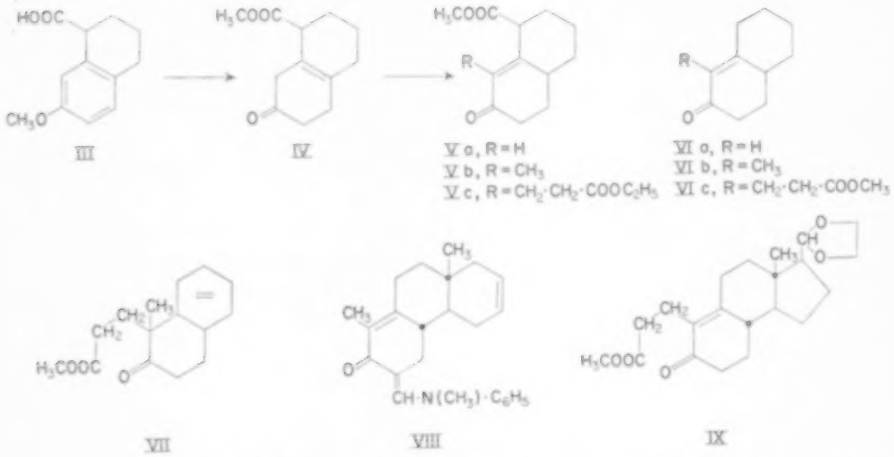
I II

ideal for the purpose of this study.

7-Methoxy-1,2,3,4-tetrahydronaphthoic acid (III), the starting material for preparation of the bicyclic unsaturated keto ester (Va), was first synthesized by Fieser and Holmes[3] and later by Hey and Nagdy.[4] This has now been prepared in an improved yield by modification (*vide* Experimental) of the method adopted by the latter workers. The acid (III) was reduced by Birch's method[5] as modified by Wilds

[1] [a] A. R. Pinder and R. Robinson, *J. Chem. Soc.* 1224 (1952); [b] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Amer. Chem. Soc.* **73**, 2403 (1951); **74**, 4223 (1952); [c] L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, *Ibid.* **76**, 5014 (1954); [d] L. B. Barkley, W. S. Knowles, H. Raffelson and Q. E. Thompson, *Ibid.* **78**, 4111 (1956); [e] D. K. Banerjee, S. Chatterjee and S. P. Bhattacharya, *Ibid.* **77**, 408 (1955).
[2] L. I. Smith and G. F. Ronalt, *J. Amer. Chem. Soc.* **65**, 631 (1943); G. Stork and A. Burgstahler, *Ibid.* **73**, 3544 (1951); H. H. Inhoffen and E. Prinz, *Chem. Ber.* **87**, 684 (1954); E. Adlerova, L. Norak and M. Protiva, *Coll. Czech. Chem. Comm.* **23**, 681 (1958).
[3] L. F. Fieser and H. L. Holmes, *J. Amer. Chem. Soc.* **58**, 2319 (1936).
[4] D. H. Hey and K. A. Nagdy, *J. Chem. Soc.* 1894 (1953).
[5] A. J. Birch, *Quart. Rev.* **4**, 69 (1950).

and Nelson.[6] No attempt was made to isolate the intermediate dihydro derivative which was hydrolysed with 5 per cent sulphuric acid in chloroform solution, and the resulting product was esterified with diazomethane. The colourless liquid, thus obtained, did not show any ultra-violet absorption maximum characteristic of the Hagemann ester system[7] and was assigned the structure IV. This was justified by its conversion to the α,β-unsaturated keto ester (Va) by treatment with methanolic hydrogen chloride. The compound (Va) showed ultra-violet absorption maximum at 236 mμ (log ϵ 4·07) with a small hump at 280 mμ, the latter probably indicating the presence of a trace of methyl 7-methoxy-1,2,3,4-tetrahydronaphthoate. Treatment of IV with methanol containing a few drops of hydrochloric acid according to Wild's procedure[8] furnished Δ^{1-9}-octalone-2 (VIa) as the major product. Two different cosolvents, 1,2-dimethoxyethane and dioxane, were used for this reduction, the former giving a better yield.

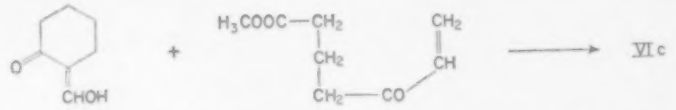


Methylation of Va was carried out with sodium hydride and methyl iodide in benzene, and the product showed the expected bathochromic shift in the ultra-violet absorption maximum. The final proof of the structure of methyl 7-keto-8-methyl-1,2,3,4,4a,5,6,7-octahydronaphthoate (Vb) was obtained by its conversion to 1-methyl-Δ^{1-9}-octalone-2 (VIb) by treatment with aqueous alkali.

In view of Barkley *et al.*[1d] work showing that, whereas Woodward's[1b] addition of acrylonitrile to the tricyclic unsaturated ketone (VIII) yielded predominantly a product with an unfavourable stereochemistry, methylation of the tricyclic unsaturated keto ester (IX) furnished stereoselectively the product with the desired configuration, alkylation of Va with ethyl β-chloropropionate was also studied. It was found that by using potassium t-butoxide in t-butanol in place of sodium hydride in benzene, methyl 7-keto-8-β-ethoxycarbonylethyl-1,2,3,4,4a,5,6,7-octahydronaphthoate (Vc) could be obtained in a better yield. The structure (Vc) assigned to the aforementioned condensation product was proved by degrading it to 1-β-methoxycarbonylethyl-Δ^{1-9}-octalone-2 (VIc) by treatment with aqueous methanolic potassium hydroxide

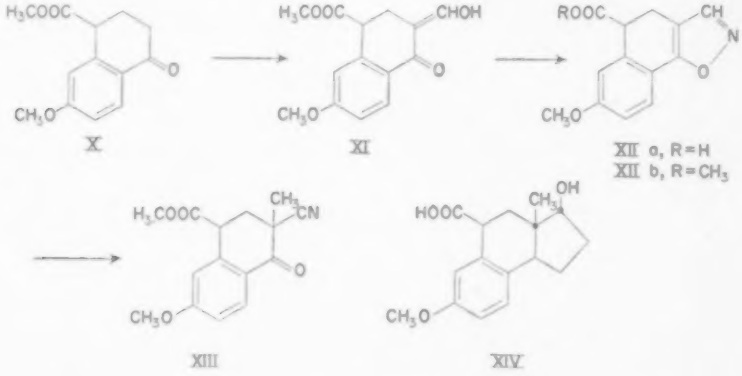
[6] A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.* **75**, 5360 (1953).
[7] R. M. Acheson and R. Robinson, *J. Chem. Soc.* 1130 (1952).
[8] A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.* **75**, 5366 (1953).

followed by esterification with diazomethane and by direct comparison of the semicarbazone of VIc with that of an authentic specimen prepared by the condensation of 2-hydroxymethylenecyclohexanone with methyl 5-keto-6-heptenoate[1d] in the presence of potassium t-butoxide in t-butanol followed by successive treatment with alkali and diazomethane. The yield was poorer when the above condensation was carried out with cyclohexanone.



Methylation of VIc following the procedure of Barkley *et al.*[1d] furnished a mixture of a 1-methyl-1-β-methoxycarbonylethyloctalone-2 (VII) and the starting material which could be separated on an acid washed alumina column. The structure of the former was deduced from the absence of the characteristic ultra-violet absorption maximum of an α,β-unsaturated ketone.

The methyl ester (X) of 4-keto-7-methoxy-1,2,3,4-tetrahydronaphthoic acid, an intermediate in the preparation of 7-methoxy-1,2,3,4-tetrahydronaphthoic acid (III) by the method of Hey and Nagdy,[4] was converted into methyl 3-methyl-3-cyano-4-keto-7-methoxynaphthoate (XIII) via the hydroxymethylene derivative (XI) and the isoxazoles (XIIa and XIIb) following the procedure of Johnson *et al.*[9] Our future programme consists in the stereospecific conversion of the keto cyano ester (XIII) by the method of Banerjee *et al.*[10] into the benzohydrindane derivative (XIV), which in the context of present investigation may be regarded as an important intermediate for the synthesis of testosterone.



EXPERIMENTAL*

7-Methoxy-1,2,3,4-tetrahydronaphthoic acid (III)

m-*Methoxybenzyl alcohol.* Previously prepared from *m*-methoxybenzaldehyde by electrolytic reduction by Rapson and Robinson[11] in 56% yield and by catalytic hydrogenation by Woodward[12]

* All melting and boiling points are uncorrected, and all ultra-violet measurements were taken in 95% ethanol and with Beckmann Quartz Ultraviolet Spectrophotometer, Model DU.

[9] W. S. Johnson, J. W. Petersen and C. D. Gutsche, *J. Amer. Chem. Soc.* **69**, 2942 (1947).
[10] D. K. Banerjee, S. Chatterjee, C. N. Pillai and M. V. Bhatt, *J. Amer. Chem. Soc.* **78**, 3769 (1956).
[11] W. S. Rapson and R. Robinson, *J. Chem. Soc.* 1537 (1935).
[12] R. B. Woodward, *J. Amer. Chem. Soc.* **62**, 1481 (1940).

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in quantitative yield. This has now been prepared by crossed Cannizzaro reaction[13] in 92·5% yield. To a stirred solution of 37·05 g of *m*-methoxybenzaldehyde and 31 cc 40% formalin in 54·5 cc of methanol at 65° was added a small portion of a solution of 45·7 g KOH in 32·6 cc water. The temp was initially maintained by external heating until the reaction started which was indicated by the rise in temperature. The exothermic reaction was then maintained at 70° by controlling the rate of addition of the alkali. After stirring for 40 min the solution was refluxed for 25 min. After cooling and dilution with water the product was extracted with ether. The extract was washed with water, the ether removed, and the residue fractionated to yield 34·75 g *m*-methoxybenzyl alcohol, b.p. 98–105° (0·8 mm); recorded b.p. 125° (12 mm)[11] and 150° (25 mm).[12]

m-*Methoxybenzyl chloride*. Prepared from *m*-methoxybenzyl alcohol by the method of Cornforth and Robinson[14] in 94% yield. When phosphorus trichloride was used the yield was lower (69%), and no action was observed with dry hydrogen chloride in benzene.

m-*Methoxyphenylacetonitrile*. Prepared from *m*-methoxybenzyl chloride by the method of Rapson and Robinson[11] except that ethanol was replaced by acetone as solvent, and a higher yield (93·5%) was obtained. Hey and Nagdy[4] prepared this compound from *m*-methoxybenzaldehyde by the hippuric acid method in 23% yield. Overall yield in our case from the same starting material was 71%.

Ethyl m-*methoxyphenylcyanoacetate*. Previously prepared by the condensation of *m*-methoxyphenylacetonitrile with diethyl carbonate in the presence of sodium dust in ether by Hey and Nagdy[4] following the procedure of Niederl and Roth.[15] Considerable improvement in the yield of this product has now been achieved by introducing the following modification. To a cooled and stirred mixture of 3·9 g sodium hydride, 50 cc benzene and 19·2 cc diethyl carbonate under 1 atm nitrogen, was added a solution of 23 g *m*-methoxyphenylacetonitrile in 15 cc benzene at such a rate that the reaction was never too vigorous. The reaction mixture was allowed to stand overnight, and the solid cake formed decomposed with iced HCl under nitrogen with cooling. The organic layer was separated and washed with water. After removal of the solvent the residue was fractionated *in vacuo* to yield 6·4 g unchanged *m*-methoxyphenylacetonitrile and 21·5 g (87% on the basis of recovered material) ethyl *m*-methoxyphenylcyanoacetate, b.p. 156–157° (1·5 mm); recorded[4] 120–125° (5×10^{-3} mm).

Diethyl α-(m-*methoxyphenyl*)-α-*cyanoglutarate*

To a solution of sodium ethoxide, prepared from 0·05 g sodium in 10 cc ethanol, was added 21·3 g ethyl *m*-methoxyphenylcyanoacetate. To this mixture was then added with swirling 11 cc methyl acrylate at such a rate that the temp was maintained at 50–55°. After standing for 2 hr a few drops of acetic acid were added and the product worked up after dilution with water in the usual manner to yield 1·5 g unchanged material and 26·8 g (84%) diethyl α-(*m*-methoxyphenyl)-α-cyanoglutarate, b.p. 185–188° (1·7 mm). Floyd and Miller[16] also observed similar ester exchange during the addition of methyl acrylate to alkylmalonic esters. (Found: C, 63·9; H, 6·9. Calc. for $C_{17}H_{21}NO_6$: C, 63·9; H, 6·6%).

α-(m-*Methoxyphenyl*)*glutaric acid*. Prepared by refluxing for 24 hr a mixture of 26·6 g diethyl α-(*m*-methoxyphenyl)-α-cyanoglutarate, 100 cc conc HCl and 100 cc water. The ethereal extract on evaporation furnished 18·44 g (90%) α-(*m*-methoxyphenyl)glutaric acid, m.p. 120–121°. On crystallization from dil HCl the product melted at 120·5–121°. Hey and Nagdy[4] prepared the same compound, m.p. 121–122°, by the hydrolysis of ethyl α,γ-dicyano-α-*m*-methoxyphenylbutyrate in 72% yield. (Found: C, 60·5; H, 6·0. Calc. for $C_{13}H_{14}O_5$: C, 60·5; H, 5·9%).

7-*Methoxy*-4-*keto*-1,2,3,4-*tetrahydronaphthoic acid*. Previously prepared by Hey and Nagdy[4] from the aforementioned glutaric acid by cyclodehydration with hydrogen fluoride in 86% yield. This has now been prepared by a different method but in a lower yield. To a stirred cold solution of 10 g α-(*m*-methoxyphenyl)glutaric acid in 30 cc benzene was added 20 g finely powdered phosphorous pentachloride. After cooling in an ice-bath, the acid chloride was treated with a chilled solution of 11 cc stannic chloride in 75 cc benzene. After standing for 15 min the product was poured into ice. The organic layer was separated and washed thoroughly with water. After removal of the

[13] D. Davidson and M. T. Bogert, *J. Amer. Chem. Soc.* **57**, 905 (1935).
[14] J. W. Cornforth and R. Robinson, *J. Chem. Soc.* 686 (1942).
[15] J. Niederl, R. J. Roth and A. A. Plentl, *J. Amer. Chem. Soc.* **59**, 1901 (1937); J. Niederl and R. J. Roth, *Ibid.* **60**, 2140 (1938).
[16] D. E. Floyd and S. E. Miller, *J. Org. Chem.* **16**, 883 (1951).

solvent the solid residue was crystallized from dilute acetic acid to furnish 7-methoxy-4-keto-1,2,3,4-tetrahydronaphthoic acid, m.p. 151–153°; recorded[4] 155°, in 76% yield.

7-Methoxy-1,2,3,4-tetrahydronaphthoic acid (III). This was obtained by Hey and Nagdy[4] by reduction of the aforementioned keto acid by the Clemmensen method in 53% yield. An improved yield was obtained when the reduction was carried out by Huang-Minlon's[17] method. A mixture of 1·95 g of the above keto acid, 2·55 g KOH in 25 ml diethylene glycol and 2·5 ml 50% hydrazine hydrate was heated for 2 hr at 135° (inner temp). The temp of the mixture was raised to 195–200° by allowing the vapours to escape and maintained at that point for 2 hr. The cooled solution was diluted and treated with 4·5 ml dimethyl sulphate at 70–75° with shaking. Potassium hydroxide (5 g) was then added and the mixture heated for 1 hr on the steam bath. The cooled solution was filtered into an excess HCl and 1·7 g (93%) of the crude acid, m.p. 130–132°, obtained. After purification by short-path distillation and crystallization from ether–pet ether (40–60°) the product melted at 137–138°; recorded[4] 137–138°.

Methyl 7-keto-1,2,3,4,4a,5,6,7-octahydronaphthoate (Va)*

To a solution of 5 g 7-methoxy-1,2,3,4-tetrahydronaphthoic acid (III) in 40 ml dry 1,2-dimethoxyethane was added 1·5 l. anhydrous liquid ammonia. To the above stirred mixture was then added within 5 min, 5 g metallic lithium, cut into small pieces. After stirring for 10 min, 150 ml ethanol was added fairly rapidly when the blue colour was discharged. The ammonia was allowed to evaporate and the mixture neutralized with cooling and stirring by dropwise addition of conc H_2SO_4. Chloroform (40 ml) and then enough conc H_2SO_4 to make the solution 5% by volume was slowly added, and the mixture stirred at room temp for 18 hr. The chloroform layer was separated and the aqueous layer thoroughly extracted with chloroform. The combined chloroform layer after washing with water was dried. The brown syrupy residue, obtained after removal of the solvent, was treated with an ethereal solution of diazomethane, prepared from 5 g nitrosomethylurea. After 5 min the excess diazomethane was destroyed by addition of glacial acetic acid. The ethereal solution was successively washed with water, cold KOH solution and water. Removal of the solvent and distillation of the residue *in vacuo* furnished 4·4 g of an oil, b.p. 90–150° (2 mm). On refractionation a sample of (IV) for analysis was collected at 140° (2 mm); n_D^{23} 1·5072; d_4^{22} 1·130. (Found: C, 69·4; H, 8·3; mol refractivity, 54·8. Calc. for $C_{12}H_{16}O_3$: C, 69·2; H, 7·7%; mol refractivity, 54·4).

The β,γ-unsaturated keto ester (IV, 21·8 g) was refluxed for 4 hr with methanolic hydrogen chloride (11 g hydrogen chloride in 600 ml methanol). The methanol and the hydrogen chloride were removed under suction, and the residue distilled to give 12·2 g methyl 7-keto-1,2,3,4,4a,5,6,7-octahydronaphthoate (Va), b.p. 145–150° (1·5–2 mm); n_D^{23} 1·5140. (Found: C, 69·7; H, 7·7. Calc. for $C_{12}H_{16}O_3$: C, 69·2; H, 7·7%).

The *semicarbazone* of Va crystallized from alcohol, m.p. 199–200° (dec); λ_{max} 269 mμ, log ϵ 4·48. (Found: N, 15·7. Calc. for $C_{13}H_{19}N_3O_3$: N, 15·9%).

A reduction of 2 g of the acid (III) in 25 cc dimethoxyethane and 500 cc anhydrous ammonia with 2·1 g lithium metal gave 1·9 g (IV), which was refluxed with 25 cc dry methanol and 0·6 cc conc HCl for 4 hr. The removal of methanol under diminished pressure and evaporative distillation of the residue gave 1·18 g Δ^{1-9}-octalone-2 (VIa); b.p. 120–130° (1·5 mm); λ_{max} 238 mμ, log ϵ 3·95. The semicarbazone melted at 205° (dec); recorded 214,[16] 215,[18] 208.[19] (Found: N, 20·00. Calc. for $C_{11}H_{17}N_3O$: N, 20·3%).

Methyl 7-keto-8-methyl-1,2,3,4,4a,5,6,7-octahydronaphthoate (Vb)

To a stirred mixture of 0·58 g sodium hydride and 100 ml benzene was added a solution of 5 g methyl 7-keto-1,2,3,4,4a,5,6,7-octahydronaphthoate (Va) in 50 ml benzene under 1 atm nitrogen. After stirring for 24 hr, 35 g methyl iodide was added and the stirring continued for a further 24 hr. The mixture was finally refluxed for 7 hr. To the cooled reaction mixture ice-cold water was added under nitrogen and the mixture extracted with ether–benzene. The extract was washed with water, the solvent removed and the residue distilled to furnish 3·5 g Vb, b.p. 128–130° (0·9 mm); n_D^{25}

* Wild and Nelson's procedure (*loc. cit.*) was made available to us through the courtesies of Dr. W. S. Johnson and Dr. A. L. Wilds before its publication.

[17] Huang-Minlon, *J. Amer. Chem. Soc.* **68**, 2487 (1946).
[18] A. J. Birch, *J. Chem. Soc.* 434 (1944).
[19] E. C. Du Feu, F. J. McQuillin and Robert Robinson, *J. Chem. Soc.* 53 (1937).

1·5098; λ_{max} 246–247 mμ, log ε 3·73. (Found: C, 70·8; H, 8·1. Calc. for $C_{13}H_{18}O_3$: C, 70·3; H, 8·1%).

The *semicarbazone* crystallized from alcohol, m.p. 213–215° (dec); λ_{max} 271 mμ, log ε 4·45. (Found: N, 15·4. Calc. for $C_{14}H_{21}N_3O_3$: N, 15·1%).

Conversion of methyl 7-keto-8-methyl-1,2,3,4,4a,5,6,7-octahydronaphthoate (Vb) *to 1-methyl-*Δ^{1-9}*-octalone-2* (VIb)

To a solution of 0·8 g of the keto ester (Vb) in 8·5 ml ethanol was added a solution of 0·9 g KOH in 1·5 ml water, and the mixture was refluxed for 7 hr under nitrogen. The cooled solution was diluted with water and extracted with benzene. The extract was washed with dilute alkali and then with water. After removal of the solvent the residue on distillation furnished 0·25 g of the methyl-octalone (VIb), b.p. 95–100° (2·5 mm); λ_{max} 248 mμ, log ε 4·1; recorded[14] λ_{max} 249, log ε 4·1. The *semicarbazone* melted at 210–212° (dec); recorded[14] 212° (dec). Admixture with an authentic specimen did not depress the melting point.

*Methyl 7-keto-8-*β*-ethoxycarbonylethyl-1,2,3,4,4a,5,6,7-octahydronaphthoate* (Vc)

To a cold solution of potassium t-butoxide in t-butanol, from 1·2 g of potassium and 45 ml t-butanol, was added a solution of 6 g of the keto ester (Va) in 12·5 ml t-butanol. After standing at the room temp for 3 hr, 4·65 g ethyl β-chloropropionate was added with cooling in ice. The mixture was refluxed for 18 hr. To the cooled reaction mixture was added 2 ml glacial acetic acid, and then most of the t-butanol was removed under suction. After addition of water the product was extracted with ether. The ether extract was washed with 2% cold KOH solution and water. After removal of the ether and fractionation of the residue 5·6 g of the keto diester (Vc), b.p. 130–145° ($1·4 \times 10^{-2}$ mm); λ_{max} 245 mμ, log ε 4·1, was obtained. (Found: C, 66·3; H, 7·8. Calc. for $C_{17}H_{24}O_5$: C, 66·2; H, 7·8%). The *semicarbazone* crystallized from ethanol, m.p. 157–159°; λ_{max} 272 mμ, log ε 4·5. (Found: N, 11·9. Calc. for $C_{18}H_{27}N_3O_5$: N, 11·5%).

*Conversion of methyl 7-keto-8-*β*-ethoxycarbonylethyl-1,2,3,4,4a,5,6,7-octahydronaphthoate* (Vc) *to 1-*β*-methoxycarbonylethyl-*Δ^{1-9}*-octalone-2* (VIc)

A mixture of 13·3 g of the unsaturated keto diester (Vc) and a solution of 6 g KOH in 10 ml water and 60 ml methanol was refluxed for 3 hr. The acidic material isolated in the usual way was esterified with diazomethane. On fractionation 7·6 g of the unsaturated keto ester (VIc), b.p. 138–140° (0·8 mm); λ_{max} 247–249 mμ, log ε 4·2, was obtained. (Found: C, 71·4; H, 8·7. Calc. for $C_{14}H_{20}O_3$: C, 71·2; H, 8·5%). The *semicarbazone* crystallized from dilute alcohol, m.p. 158–160°; λ_{max} 271–272 mμ, log ε 4·5. The aforementioned melting point was not depressed on admixture with an authentic specimen, m.p. 160–163°. (Found: N, 14·7. Calc. for $C_{15}H_{23}N_3O_3$: N, 14·3%).

*Preparation of the authentic specimen of 1-*β*-methoxycarbonyl-*Δ^{1-9}*-octalone-2* (VIc)

(a) To a solution of potassium t-butoxide, prepared from 0·5 g potassium and 30 ml t-butanol, was added a mixture freshly distilled 10 g 2-hydroxymethylenecyclohexanone and 17·7 g methyl 3-keto-Δ^1-heptenoate[14] in 10 ml t-butanol. After standing overnight, the reaction mixture was acidified with dil acetic acid and extracted with ether. The extract was washed with water and the ether removed. The residue was stirred with a solution of 28 g KOH in 2 l. dioxan–water (1 : 1) mixture. After acidification the product was worked up by extraction with ether in the usual way and esterified with diazomethane. Distillation *in vacuo* furnished 6·2 g of the unsaturated keto ester (VIc), b.p. 150° (1 mm); λ_{max} 247–249 mμ, log ε 4·2. (Found: C, 70·9; H, 8·6. Calc. for $C_{14}H_{20}O_3$: C, 71·2; H, 8·5%). The *semicarbazone* melted at 160–162°.

(b) When an experiment was carried out with 40 g cyclohexanone, 0·5 g potassium in 75 ml t-butanol and 30 g methyl 3-keto-Δ^1-heptenoate following the aforementioned procedure except that the ring closure and esterification were carried out with aqueous sodium hydroxide[14] and methanolic hydrogen chloride respectively, 2·8 g of the unsaturated keto ester (VIc) was obtained.

*1-Methyl-1-*β*-methoxycarbonylethyloctalone-2* (VII)

To a solution of 7·7 g of the unsaturated keto ester (VIc) in 80 ml t-butanol at 45° was added all at once a solution of potassium t-butoxide, prepared from 2 g potassium and 60 ml t-butanol, and

then within few minutes a solution of 15 ml methyl iodide in 10 ml t-butanol. The mixture was refluxed for 2½ hr, cooled and then treated with dil acetic acid. The product was extracted with ether, and the extract washed with water, cold dil KOH solution and water. Removal of the solvent and distillation of the residue furnished 7·5 g of a product boiling at 160–165° (2 mm). A solution of 3·4 mg of this product per litre of 95% ethanol showed an optical density of 0·333 at 245 mμ. It was then chromatographed on a column of acid washed alumina (300 g). Elution with pet ether (40–60°)–benzene (9 : 1) mixture followed by distillation furnished 3·23 g 1-methyl-1-β-methoxycarbonylethyloctalone-2 (VII), b.p. 155–160° (1 mm), which did not show any ultra-violet absorption maximum characteristic of α,β-unsaturated ketone. Elution with 1 : 1 mixture of pet ether (40–60°) and benzene followed by distillation gave 2·55 g of the unchanged unsaturated keto ester (VIc). (Found: C, 72·2; H, 8·6. Calc. for $C_{12}H_{22}O_3$: C, 72·0; H, 8·8%).

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Methyl 7-methoxy-4-keto-1,2,3,4-tetrahydronaphthoate (X)

A mixture of 4·3 g 7-methoxy-4-keto-1,2,3,4-tetrahydronaphthoic acid, 75 cc dry methanol and 5 cc of conc H_2SO_4 was refluxed for 16 hr. This was cooled and poured into ice and water. The separated oil was taken up in ether and the aqueous layer extracted four times with ether–benzene mixture. The combined extract was washed with water, sodium bicarbonate solution and water. The solvent was removed and the residue distilled to furnish 4·4 g (96%) methyl 7-methoxy-4-keto-1,2,3,4-tetrahydronaphthoate (X), b.p. 180–185° (2 mm), as a colourless mobile liquid. (Found: C, 66·8; H, 6·1. Calc. for $C_{12}H_{14}O_4$: C, 66·7; H, 6·0%).

6-Methoxy-4-methoxycarbonyl-3,4-dihydronaphtha-(2,1d)-isoxazole (XIIb)

To an ice-cold stirred suspension of freshly prepared sodium methoxide (from 2·3 g sodium and 4 cc dry methanol) in 25 cc dry benzene under nitrogen, was added first 14 cc ethyl formate and then, after 15 min, 11 g of the keto ester (X), in 25 cc dry benzene. After standing at room temp for 15 hr, the reaction mixture was cooled and treated with ice and water, the aqueous layer was separated and the benzene solution thoroughly extracted with ice cold 2% NaOH solution. The combined aqueous solution, after extraction with ether was acidified with iced HCl, and the precipitated oil worked up in the usual manner to give 11·5 g of the crude hydroxymethylene derivative (XI) as a gum, which gave intense violet colour with alcoholic ferric chloride solution.

A solution of the aforementioned crude hydroxymethylene derivative in 200 cc glacial acetic acid was treated with 3·5 g dry powdered hydroxylamine hydrochloride as described by Johnson *et al.*[9] to yield 11·65 g of a reddish gummy isoxazole, which was found to be a mixture of XIIa and XIIb. This was taken up in a mixture of 120 cc glacial acetic acid and 24 cc conc HCl and refluxed for 30 min. The solid obtained, on removal of the volatile materials under diminished pressure, was treated with sodium bicarbonate solution and filtered. The filtrate on acidification gave 10·3 g (89%) white crystalline *6-methoxy-4-carboxy-3,4-dihydronaphtha-(2,1d)isoxazole* (XIIa), m.p. 188–190°; recrystallized from methanol, m.p. 190°. (Found: C, 64·0; H, 4·9. Calc. for $C_{13}H_{11}O_4N$: C, 63·70; H, 4·5%).

The above acid (XIIa, 10·3 g) in 50 cc methanol was esterified with diazomethane to yield 10 g (91%) of the isoxazole ester (XIIb), m.p. 77–78°. (Found: N, 5·6. Calc. for $C_{14}H_{13}O_4N$: N, 5·4%).

Methyl 7-methoxy-4-keto-3-methyl-3-cyano-1,2,3,4-tetrahydronaphthoate (XIII)

A solution of potassium t-butoxide (from 1·7 g potassium and 42·5 cc dry t-butanol) under nitrogen was treated with 10 g 6-methoxy-4-carbomethoxy-3,4-dihydronaphtha-(2,1d)-isoxazole (XIIb) in 40 cc t-butanol and 14 cc methyl iodide as described by Johnson *et al.*[9] to give 9·5 g (90%) methyl 7-methoxy-4-keto-3-methyl-3-cyano-1,2,3,4-tetrahydronaphthoate (XIII), which on crystallization from aqueous methanol melted at 110°. (Found: C, 65·8; H, 5·8. Calc. for $C_{15}H_{15}O_4N$: C, 65·9; H, 5·5%).

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STUDIES IN SESQUITERPENES—XVI*

ZERUMBONE, A MONOCYCLIC SESQUITERPENE KETONE†

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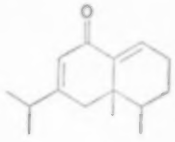
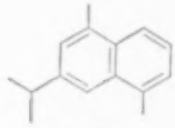
Abstract—The structure, previously assigned to zerumbone, has been found to be untenable. The ketone has been shown to be monocyclic containing three ethylenic linkages, and has been further correlated with humulene. Results from ozonolysis, and base-catalysed cleavage allow the compound to be formulated as 2,6,9,9-tetramethyl-2,6,10-cyclo-undecatrien-1-one.

THE isolation of a sesquiterpene ketone (m.p. 67–68°), $C_{15}H_{22}O$, from the rhizomes of *Zingiber zerumbet* (Sanskrit–Sthulagranthi; Hindi–Narkachur) was first described by Varier.[1] From another species (*Zingiber amaricans*; Lampoejang pait‡) of the same family van Romburgh[2] had earlier isolated a crystalline fraction, which was later studied in some detail by van Veen,[3] who declared it to be a mixture of ketones (m.p. 62–68°). From a comparison of several derivatives, it was suspected by Varier that the two products may be identical. Parihar and Dutt,[4,5] apparently, studied the ketone from *Zingiber zerumbet* in considerable detail and proposed the structure (I) for this new ketone, which was named zerumbone. The structure (I) rested chiefly on the selenium dehydrogenation of tetrahydrozerumbol to eudalene. Since no proof for the location of the carbonyl group had been given, it was decided to fix its position by dehydrogenation of a suitable precursor, when according to structure (I), 5-methyleudalene (II) should be obtained. As a matter of fact, no



I



II

picrate-forming material could be isolated from such a reaction and further, on repetition of dehydrogenation of tetrahydrozerumbol or its dehydration product we failed to detect the formation of eudalene.§ In view of this and other apparent

*Part XV: *J. Ind. Chem. Soc.* **34**, 255 (1957).

† A preliminary report appeared in *Chem. & Ind.* 1051 (1956).

‡ van Veen[3] states that according to K. Heyne 'Lampoejang pait' is *Zingiber amaricans* and not *Zingiber zerumbet* as described by van Romburgh.

§ This observation removed the apparent discrepancy between zerumbone and the ketone of van Veen, as he had shown earlier that his ketone does not belong to any naphthelenic system. This author carried out most of the reactions on the ketone fraction, m.p. 68°, and it is clear now that, at least, this particular fraction is identical with zerumbone.

[1] N. S. Varier, *Proc. Ind. Acad. Sci.* **A 20**, 257 (1944).
[2] P. van Romburgh, *Teysmannia* 561 (1902).
[3] A. G. van Veen, *Rec. Trav. Chim. Pays-Bas* **58**, 691 (1939).
[4] D. B. Parihar and S. Dutt, *Ind. Soap J.* **16**, 123 (1950).
[5] D. B. Parihar and S. Dutt, *Ind. Soap J.* **16**, 145 (1950).

contradictions in their own work, a systematic reinvestigation, ignoring the work of these authors* was undertaken.

The relevant features of the previous work carried out by van Veen[3] and Varier[1] may briefly be summarized as follows. With hydrogen sulphide in an ammonical ethanolic solution, zerumbone gave an addition compound and from this it was suspected[1] that zerumbone is an $\alpha\beta$-unsaturated ketone. On catalytic reduction it gave a tetrahydroketone.[1] van Veen on the other hand, on prolonged hydrogenation obtained a mixture of hydrogenation products from which a solid, m.p. 60°, and considered by him to have the formula $C_{15}H_{30}O$ (hence acyclic), could be isolated in a low yield. Wolff–Kishner reduction of zerumbone semicarbazone gave an impure sample of a monocyclic hydrocarbon.[3]

Zerumbone displayed its ultra-violet absorption peaks at 248 mμ (ε 8480) and 325 mμ (ε 250), a shoulder around 233 mμ (ε 8000) was also quite marked. The position of the *K*-band is in conformity with either an $\alpha\beta$-olefinic carbonyl[6] or a cross-conjugated dienone chromophore;[7] a decision in favour of the latter possibility could be made on the basis of the evidence described in the sequel. In the infra-red (in carbon tetrachloride) it showed bands at 1662 with slight shoulders around 1650 and 1635 cm^{-1} ($\alpha\beta$-unsaturated ketone and ethylenic linkage; possibly a conjugated dienone),[8] this band was broader and a little better resolved in Nujol (1658, 1650 and 1635 cm^{-1}); other bands at 1390 and 1370 (*gem*-dimethyl group), 970 (*trans-sym*-disubstituted ethylenic linkage) and 830 cm^{-1} (trisubstituted ethylenic linkage) were also prominent in both the spectra.

Lithium aluminium hydride reduction of zerumbone gave the corresponding alcohol (zerumbol), which regenerated the ketone on either manganese dioxide oxidation or Oppenauer oxidation. Sodium–alcohol reduction of zerumbone, produced a mixture of epimeric alcohols, separable via their 3:5-dinitrobenzoates into a liquid (α-epimer) and a crystalline (β-epimer) isomer. Pydridine–chromic acid oxidation of the α-alcohol gave tetrahydrozerumbone, described below. Catalytic reduction of zerumbone in alcoholic solution in the presence of Pd-$CaCO_3$ catalyst led to the uptake of two moles of hydrogen to give tetrahydrozerumbone (λ_{max}^{EtOH} 281 mμ, ε 39), which on lithium aluminium hydride reduction gave the same mixture of epimeric alcohols; reduction with aluminium isopropoxide in isopropanol gave the single crystalline β-epimer. It is clear from these observations that during the sodium–alcohol reduction of zerumbone, two ethylenic linkages, which must be conjugated with the keto group got reduced simultaneously to give tetrahydrozerumbols. These results, taken in conjunction with the ultra-violet data of zerumbone, establish the presence of a cross-conjugated dienone chromophore in the terpenoid; the position of the λ_{max} further indicated that the dienone chrompohore may have the di-transoid geometry.[9]

On treatment with alkali, zerumbone underwent reversal of aldol condensation to produce methyl ethyl ketone as the only volatile product, which together with the

* A report, containing the above results and also the evidence for its monocyclic nature was first made by the present author to the Council of the Indian Institute of Science, Bangalore, in 1951–55 (Forty-third Annual Report); however, the work could not be continued then for several reasons. Also cf. V. K. Balakrishnan, R. K. Razdan and S. C. Bhattacharyya, *Perf. and Essent. Oil Rec.* **47**, 274 (1956).

[6] R. B. Woodward, *J. Amer. Chem. Soc.* **63**, 1123 (1941); **64**, 70 (1942).
[7] L. Ruzicka, S. L. Cohen, M. Furter and F. Ch. van der Sluys-Veer, *Helv. Chim. Acta* **21**, 1735 (1938).
[8] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*. Methuen, London (1954).
[9] G. G. Allan, M.B.E. Fayez, F. S. Spring and Robert Stevenson, *J. Chem. Soc.* 459 (1956).

information mentioned above, pointed to the probable occurrence of the unit (III) in the ketone.

Tetrahydrozerumbone and the two tetrahydrozerumbols still contain an olefinic linkage (yellow colour with tetranitromethane). On further catalytic hydrogenation in glacial acetic acid in the presence of Adam's catalyst, tetrahydrozerumbone took up one mole of hydrogen to provide a mixture of saturated ketones (no colour with tetranitromethane). By repeated crystallizations, one pure isomer of hexahydrozerumbone (λ_{max}^{EtOH} 288 mμ, ε 27·5) could be obtained. Thus zerumbone contains three ethylenic bonds and it follows, then, from its molecular formula ($C_{15}H_{22}O$) that it is monocyclic.

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Since tetrahydrozerumbone gave a mixture of hexahydrozerumbones, the olefinic linkage must have at least one of its carbon atoms fully substituted. An asymmetric di-substituted ethylenic bond could hardly be expected to escape hydrogenation under the conditions of formation of tetrahydrozerumbone and hence, the olefinic bond in the tetrahydroketone must be at least trisubstituted. This is supported by the absence of any strong absorption around 890 cm^{-1} in the infra-red spectra of both zerumbone and its tetrahydro derivative. A decision between the trisubstituted and the tetrasubstituted ethylenic linkage could be made on the basis of the end-absorption[10–12] of this linkage in tetrahydrozerumbone and tetrahydrozerumbyl acetate (mixture of epimers). It is clear from the data (Table 1) that the double bond is trisubstituted.

TABLE 1. END ABSORPTION

	ε_{210}	ε_{215}	ε_{220}	ε_{225}
Tetrahydrozerumbone*	2740	1700	1145	820
Tetrahydrozerumbyl acetate	3195	1690	980	810
Trisubstituted olefinic linkage[10]	1400–4700	600–3500	250–1800	—
Tetrasubstituted olefinic linkage[10]	4400–10,000	3900–9200	3400–6700	—

* On Cary recording spectrophotometer it showed apparent λ_{max} 201 mμ, ε 4500.

This finding is further supported by the presence of bands in the infra-red spectrum (pure liquid) of tetrahydrozerumbone at 818 and 845 cm^{-1}.

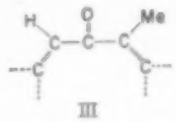
The C=O stretching frequency* for tetrahydrozerumbone (1700 cm^{-1}; liquid) and hexahydrozerumbone (1698 cm^{-1}; solid film) pointed to the interesting conclusion that the carbonyl group is situated in a ring which is possibly larger than seven-membered;[8,†] a comparison with the C=O stretching frequencies in medium

* Determined precisely on a Perkin–Elmer Model 112 spectrophotometer (single beam) with a sodium chloride prism. Author is grateful to Mr. B. R. Lakshmanan for these measurements.

† Some cyclohexanones do exhibit their $\nu^{C=O}$ in this range, but all such compounds are highly alkylated on both the carbon atoms flanking the carbonyl. It would be clear from the previous discussion that such a state does not prevail in the case of tetrahydro- and hexahydrozerumbone.

[10] P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.* 2737 (1952).
[11] T. G. Halsall, *Chem. & Ind.* 867 (1951).
[12] E. Lederer, *J. Chim. Phys.* **51**, D119 (1954).

rings[13,14] revealed that zerumbone may contain such a ring. This appeared to be further supported by the fact that tetrahydrozerumbone and tetrahydrozerumbyl acetate showed a depression of molecular refraction, a property characteristic of the medium ring-size.[13,15]



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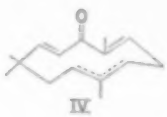

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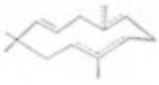

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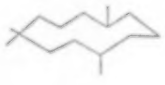
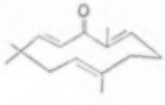


VI



VII

Taking into consideration the above information and the biogenetic isoprene rule,[16] structure (IV) appeared attractive. The fact that humulene (V), in which the presence of an eleven-membered ring[17] is now well-established,[18] is an important constituent of the essential oil of *Zingiber zerumbet*, the working structure (IV) became all the more plausible. Clemmensen reduction of hexahydrozerumbone was carried out to yield the deoxy compound, which had properties virtually identical with those of humulane (VI) (Table 2). The identity of the two compounds was

TABLE 2. PHYSICAL PROPERTIES OF HUMULANE AND DEOXYHEXAHYDROZERUMBONE

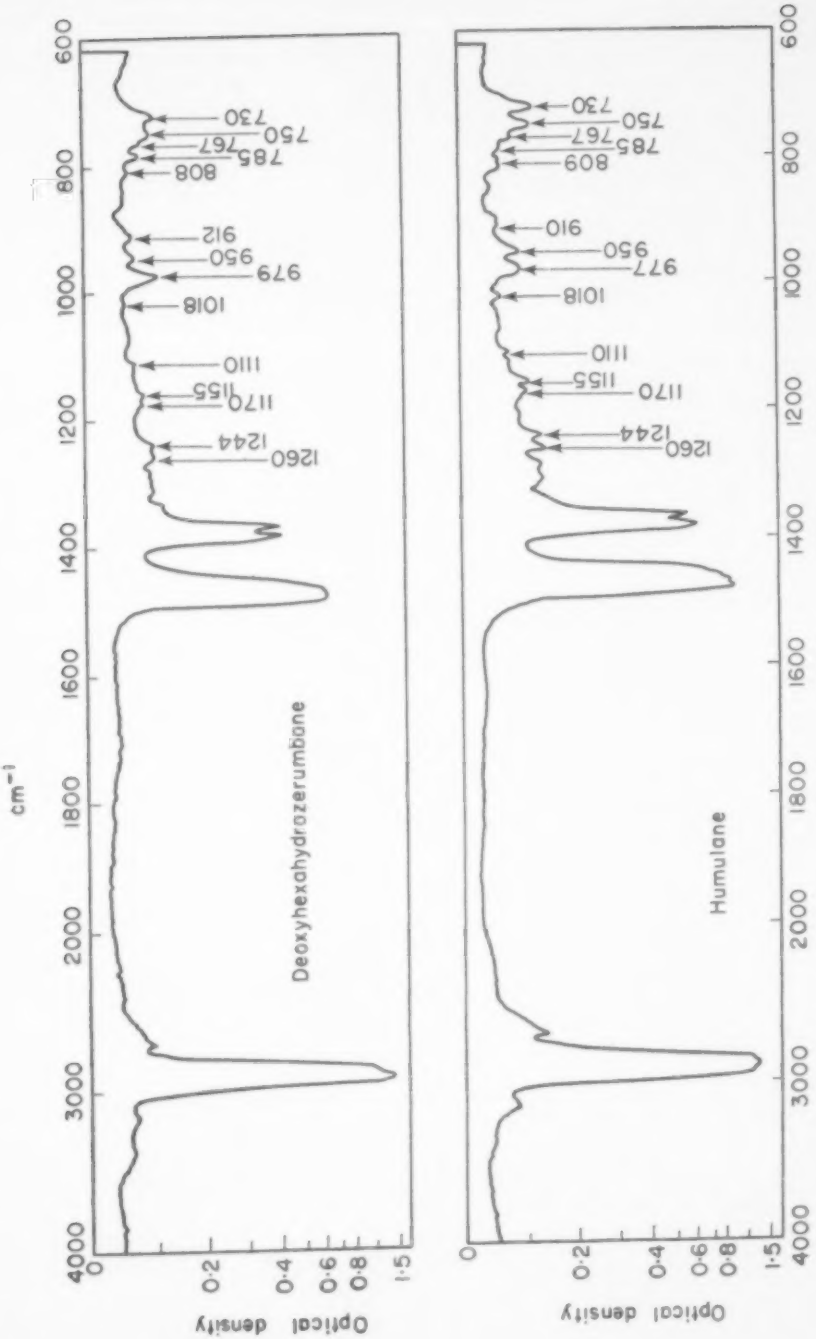
Sample	b.p./mm	$n_D/t°$	$d_4/t°$	M_D	EM_D
Deoxyhexahydrozerumbone	128–9/13	1·4720/25	0·8506/25	69·15	−0·12
Humulane*	128–9/13	1·4705/25	0·8500/25	69·00	−0·27
Humulane†	128/14	1·4720/20	0·8593/20	68·55	−0·72

* An authentic sample from humulene (*vide* Experimental).
† Data reported by F. Sorm *et al.*[18] for synthetic humulane.

confirmed by a comparison of their infra-red spectra (Figs. 1 and 2).[18,19] The small difference in the relative intensity of some of the peaks is attributable to the difference in the relative proportions of the two possible stereoisomers of 1,1,4,8-tetramethyl-cyclo-undecane; this is confirmed by the vapour-phase chromatography of the two samples (Fig. 3).

Taking humulane as the basic skeleton, the unit (III) and another unconjugated trisubstituted ethylenic linkage can be accommodated only in the structure (IV); this also accounts for the optical inactivity of the ketone. Ozonolysis of zerumbone

[13] V. Prelog, *J. Chem. Soc.* 420 (1950).
[14] F. Sorm, L. Dolejs and J. Pliva, *Coll. Czech. Chem. Comm.* **15**, 186 (1950).
[15] F. Sorm, M. Streibl, J. Pliva and V. Herout, *Coll. Czech. Chem. Comm.* **16**, 639 (1951).
[16] L. Ruzicka, *Experientia* **9**, 357 (1953).
[17] F. Sorm, M. Streibl, J. Pliva and V. Herout, *Chem. Listy* **45**, 308 (1951); **46**, 30 (1932); G. R. Clemo and J. O. Harris, *Chem. & Ind.* 799 (1951); Sukh Dev, *Curr. Sci.* **20**, 296 (1951).
[18] F. Sorm, M. Streibl, V. Jarolim, L. Novotny, L. Dolejs and V. Herout, *Coll. Czech. Chem. Comm.* **19**, 570 (1954).
[19] J. Pliva, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **16**, 164 (1951).



FIGS. 1 and 2. The spectra were taken on pure liquid (smear film) and sodium chloride optics were employed.

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was carried out to distinguish between the two possible alternatives depicted in IV, however, no identifiable product could be isolated.* On the other hand, ozonolysis of zerumbol proceeded smoothly to yield *as*-dimethylsuccinic acid and laevulinic acid. This finding fixes the structure of zerumbone as 2,6,9,9-tetramethyl-2,6,10-cyclo-undecatrien-1-one (VII). It is clear from the out-of-plane =CH deformation

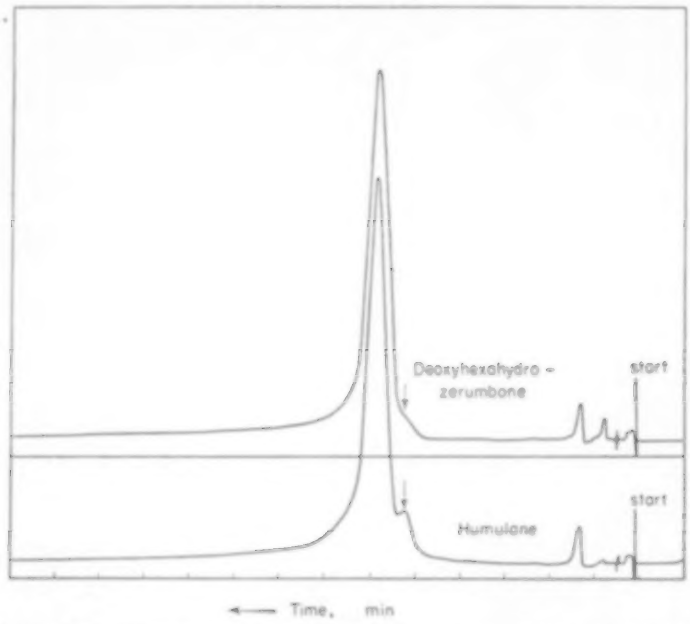

FIG. 3. The chromatography was run on a Perkin–Elmer Vapour Fractometer, Model 154B, using a 2 m column-C (Silicone oil-inert support) at 225°, with a column pressure of 28 lb/in² and flow rate of 5·0. Helium was used as the mobile phase and a 0·002 ml sample was employed in each case. This analysis was done at the Noyes Laboratories, University of Illinois, Urbana, and the author wishes to express his sincere thanks to Prof. E. J. Corey for these facilities.

vibration (970 cm^{-1}) of the C_{10}-C_{11} ethylenic linkage in zerumbone (VII) that this bond possesses the *trans*-configuration, the precise geometry of the remaining olefinic bonds must be considered as yet unsettled.

EXPERIMENTAL

All melting and boiling points are uncorrected. The ultra-violet spectra were measured in 95% ethanol (unless stated to the contrary) with a Beckman DU spectrophotometer. Infra-red spectra were (unless otherwise stated) determined with a Perkin–Elmer double-beam instrument. Pet ether refers to the fraction of b.p. 40–50°. Microanalyses were carried out by B. R. Seetharamia and D. P. Bose of this laboratory.

Isolation of zerumbone

Fully matured, raw wild ginger (*Zingiber zerumbet*) was procured from the "Kerala Soap Institute, Kozhikode" and after slicing it into thin pieces, was dried in the shade (loss of weight on drying amounted to 75%). This material on steam-distillation gave in a yield of 0·30 to 0·55% (based on the undried material) a dark oil, which almost completely crystallized out. The oil (100 g) was

* Zerumbone is a labile compound and undergoes polymerization on exposure to air to yield a gum.

taken up in pet ether (50 ml) and chilled to −5 to −10° and the solid (50 g, m.p. 60–62°) collected after 24 hr. The solid ketone was distilled (b.p. 137–141°/2·5 mm, yield 48 g) and the product crystallized once from pet ether and finally from dilute alcohol to give 40 g of colourless, flat needles (or stout prismatic rods), m.p. 66–67°.

The remaining portion of the essential oil, still containing some dissolved zerumbone, was reserved for investigation at a later date.

Zerumbone soon deteriorates at room temp (10–30 days) to give a gummy material, from which any unchanged zerumbone may be isolated by distillation; no fore-run is obtained and besides zerumbone only polymerized residue is left. The ketone is best stored as a saturated ethanolic solution in a refrigerator, where it will keep for years. In the solid state it can be preserved at 0° for a few months.

Oxime. This was prepared by the pyridine method and the product crystallized twice from dilute alcohol to yield colourless prisms, m.p. 178·5° (Lit. m.p.: 172–173°[1], 179°[8]) (Found: N, 6·3, $C_{15}H_{23}ON$ requires: N, 6·0%).

Semicarbazone was prepared by the pyridine method at room temp and was obtained in long, flat needles after two crystallizations from dil alcohol: m.p. 161·5–162·5° (Lit. m.p.: 163°[1], 155–160°[8]) (Found: N, 15·0. $C_{16}H_{25}ON_3$ requires: N, 15·3%).

Thiosemicarbazone was obtained by refluxing for 5 min a mixture of thiosemicarbazide (0·5 g), ketone (0·5 g), water (5 ml) and alcohol (10 ml). The product was collected after two days at room temp and recrystallized from dil alcohol to furnish white, feathery plates, m.p. 229·5–230·5° (efferv) (Found: N, 14·4. $C_{16}H_{25}N_3S$ requires: N, 14·4%).

2,4-*Dinitrophenylhydrazone*. The sulphuric acid method yielded a material (crude, m.p. 140–145°) which could be purified only with difficulty. It was best prepared by adding zerumbone (1·0 g) and two drops of conc HCl to a refluxing solution of 2,4-dinitrophenylhydrazine (0·9 g) in alcohol (75 ml). The clear, deep red solution, thus obtained, was left aside and the product collected after several hours (crude, m.p. 159–160°) and recrystallized twice from benzene–pet ether to give deep red prisms, m.p. 160·5–161°. (Found: N, 14·03. $C_{21}H_{26}O_4N_4$ requires: N, 14·06%).

Lithium aluminium hydride reduction of zerumbone to zerumbol

To a well-dispersed suspension of lithium aluminium hydride (0·285 g, 0·0075 mole) in anhydrous ether (25 ml), a solution of zerumbone (4·36 g, 0·02 mole) in ether (25 ml) was introduced, with cooling in an ice–salt bath, during 5 min. After stirring for 1 hr in the ice-bath, the reaction mixture was left aside as such overnight (13 hr). This was chilled in an ice–salt bath and with stirring, cautiously treated, first with 10 ml of water and then with 15 ml of 10% H_2SO_4. The ether layer was separated as soon as the complex had dissolved, and the aqueous phase extracted with pet ether (15 ml × 2). The combined extracts were washed with water, saturated aq. sodium bicarbonate solution and finally again with water and dried (sodium sulphate). The solvent was removed at room temp/suction, and the crystalline residue crystallized from pet ether at −5 to −10° to give white, prismatic needles, m.p. 77–78°, yield 2·0 g (91%). An analytical sample was crystallized once from dil alcohol and then from pet ether: m.p. 79–80° (Found: C, 81·90; H, 10·57. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%)

3,5-*Dinitrobenzoate* was obtained as white lustrous leaflets from benzene–pet ether, m.p. 119–120° (Found: N, 6·7. $C_{22}H_{26}O_6N_2$ requires: N, 6·8%).

Oxidation of zerumbol to zerumbone

(i) *Oppenauer oxidation*. A mixture of the alcohol (220 mg), cyclohexanone (980 mg), aluminium t-butoxide (396 mg) and thiophene-free benzene (5 ml) was refluxed for 15 hr and then after cooling, treated with 5% HCl (10 ml). The benzene layer was washed once with ice-cold 5% HCl, then with water and dried. The solvent was removed and the residue fractionated and the fraction, b.p. 115–120°/0·3 mm directly converted into its 2,4-dinitrophenylhydrazone by the HCl-method. The derivative was obtained from benzene–pet ether as deep red prisms, yield 60 mg, m.p. and mixed m.p. with an authentic sample was 160–161°.

(ii) *Manganese dioxide oxidation*. A solution of zerumbol (660 mg) in dry pet ether (60 ml) was stirred with active manganese dioxide[10] (6 g) under nitrogen atmosphere, for 24 hr, at room temp

[10] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1104 (1952).

(24–26°). The manganese dioxide was removed by filtration and washed with ether. Removal of the solvent from the filtrate gave a crystalline residue (550 mg, m.p. 64–65°), which was recrystallized from dil alcohol, m.p. and mixed m.p. with a genuine sample of zerumbone was 65–66°.

Sodium–alcohol reduction of zerumbone to tetrahydrozerumbols

To an ice-cooled solution of zerumbone (5·0 g) in absolute ethanol (125 ml), sodium (12·0 g) cut into small pieces was added all at once. After the vigour of the reaction had subsided, the ice-bath was removed and the reaction allowed to proceed first at room temp and later on a water-bath (1 hr) so that the vigour of the reaction was maintained. The alcohol was removed by suction and the residue cooled and diluted with water till an oily layer separated. This was taken up in pet ether–ether mixture (1 : 1; 30 ml × 3) and washed with brine and dried. The solvent was flashed off and the residue fractionated to give the alcohols as a colourless, thick oil, b.p. 123°/0·5 mm, yield 4·0 g. With tetranitromethane in chloroform it gave a yellow colour.

The *acetates* were prepared by the acetyl chloride–pyridine procedure in benzene solution at room temp. The product was obtained as a colourless, viscous liquid: b.p. 156–159°/5 mm, n_D^{28} 1·4833, d_4^{28} 0·9649, M_D 78·77 (Calc.: 79·72, $E\Sigma_D$ −0·36) (Found: C, 76·3; H, 11·2. $C_{17}H_{26}O_2$ requires: C, 76·6; H, 11·3%).

Separation of epimers. 3,5-Dinitrobenzoyl chloride (5·07 g, 0·022 mole) was added all at once to a solution of the above alcohols (3·33 g, 0·015 mole) in benzene (30 ml). This was cooled to 0° and treated with anhydrous pyridine (1 ml × 2) with swirling. The reaction mixture was heated at 55–60° for 4 hr and then left aside as such for another 36 hr at room temp (26°). This was diluted with water (25 ml) and the product taken up in ether–benzene (1 : 1), washed with saturated aqueous sodium bicarbonate and dried (sodium sulphate). The solvent was removed and the oily residue treated with pet ether (50 ml) and set aside at 0° and the product collected after a day: m.p. 108–114°, yield 4·6 g.

The above mixture of benzoates was dissolved in benzene (10 ml) and diluted with n-hexane (40 ml) and allowed to crystallize at room temp (26°). The white crystalline nodules (500 mg, m.p. 133–136°) were collected after four days and the mother liquor further diluted with n-hexane (50 cc) and a second crop (200 mg, m.p. 120–123°) obtained after same period. The two crops were combined (product A). The final mother liquor was freed of the solvent and residue crystallized from dilute acetone to give crystals, m.p. 118–122°, yield 3·0 g (product B); the mother liquor was rejected.

Product A was crystallized twice from benzene–pet ether to give white, silky needles (200 mg), m.p. 146–147°, of *α-tetrahydrozerumbyl 3,5-dinitrobenzoate* (Found: N, 6·68. $C_{22}H_{30}O_6N_2$ requires: N, 6·69%). The *α-tetrahydrozerumbol* was regenerated from 100 mg of the pure 3,5-dinitrobenzoate in ethanol (5 ml), on heating to just boiling with a solution of sodium hydroxide (50 mg in 0·1 ml of water and diluted to 2 ml with ethanol) and leaving aside at room temp for 24 hr. This was extracted with pet ether (10 ml × 3), washed with brine and dried. On removal of the solvent 60 mg of an extremely viscous syrup remained, which failed to crystallize. This was taken up in pyridine (1 ml) and oxidized with pyridine–chromic acid complex[21] (from 2 ml of pyridine and 100 mg of chromic acid) at room temp (24–26°) for 24 hr. Usual work up gave a ketone, which was isolated as its oxime, white needles (dil alcohol), m.p. 130–132°, mixed m.p. with an authentic sample (m.p. 133–134°) of *tetrahydrozerumbone oxime* (*vide infra*) was 131–132°.

Product B was thrice crystallized from acetone, when white silky needles (1 g) of *β-tetrahydrozerumbyl 3,5-dinitrobenzoate* were obtained, m.p. 142–143°, mixed m.p. with α-tetrahydrozerumbyl 3,5-dinitrobenzoate was 120–135° (Found: N, 6·70. $C_{22}H_{30}O_6N_2$ requires: N, 6·69%). The ester (500 mg), on saponification as above, yielded *β-tetrahydrozerumbol* (250 mg, m.p. 65–68°) which, after two crystallizations from pet ether, was obtained in white, fine needles, m.p. 72°, mixed m.p. with the Meerwein–Ponndorf reduction product (*vide infra*) of tetrahydrozerumbone was undepressed.

Tetrahydrozerumbone

Zerumbone (10·9 g) was hydrogenated, at room temp and pressure, in alcohol (75 ml) over pre-reduced Pd–$CaCO_3$ catalyst[22] (4 g). The hydrogen uptake came to a close after absorption of 100% of two mole equivalents of the gas, during 40–60 min. The reduction also stopped at the tetrahydro stage when Adam's PtO_2 catalyst (100 mg) was employed in an alcohol medium. The

[21] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953)
[22] M. Busch and K. Schulz, *Ber. Dtsch. Chem. Ges.* **62**, 1458 (1929).

catalyst was removed by filtration and the filtrate diluted with water, and the product taken up in pet ether. Working up gave tetrahydrozerumbone as a colourless liquid, b.p. 130°/3 mm, n_D^{24} 1·4912, yield 10·2 g. An analytical sample had b.p. 113°/1·6 mm, n_D^{29} 1·4890, d_4^{29} 0·9378, M_D 68·36. (Calc. 68·84, $E\Sigma_D$ —0·22). (Found: C, 81·28; H, 11·79. $C_{15}H_{26}O$ requires: C, 81·09; H, 11·80%). The *oxime* crystallized from dil alcohol in fine needles, m.p. 133–134° (Found: N, 5·88. $C_{15}H_{27}ON$ requires: N, 5·9%). The *semicarbazone* was obtained by the pyridine method by heating on a steam-bath for 8 hr and was twice recrystallized from dil alcohol to yield flat needles, m.p. 197–197·5° (dec) (Found: N, 15·0. $C_{16}H_{29}ON_3$ requires: N, 15·1%). 2,4-Dinitrophenylhydrazone could not be obtained under the usual conditions.

Meerwein–Ponndorf reduction of tetrahydrozerumbone

Tetrahydrozerumbone (1·1 g, 0·005 mole), aluminium isopropoxide (5·1 g, 0·025 mole) and anhydrous isopropanol (25 ml) were placed in a flask, which was connected to a one-foot Vigreux column carrying a total condensation-type still-head. The reaction mixture was heated under total reflux for 1 hr and then the reflux removed at the rate of 1 drop/1–2 min till no more acetone was formed (2–5 hr). Another 10 ml of the alcohol were distilled off, the residue cooled, and poured into ice and HCl aq., when an oil separated, which slowly crystallized out on refrigeration. The product was collected and crystallized from dil alcohol at 0° to give needles (900 mg), m.p. 66–67°; two recrystallizations at 0 to −5° from pet ether gave white, fine needles, m.p. 72°. This gave a yellow colour with tetranitromethane in chloroform solution. (Found: C, 80·1; H, 12·3. $C_{15}H_{28}O$ requires: C, 80·3; H, 12·6%). The 3,5-*dinitrobenzoate* crystallized from a mixture of benzene and pet ether in silky needles, m.p. 144°, mixed m.p. with β-tetrahydrozerumbyl 3,5-dinitrobenzoate (*vide supra*) was 143–144°. (Found: N, 6·65. $C_{22}H_{30}O_6N_2$ requires: N, 6·69%).

Lithium aluminium hydride reduction of tetrahydrozerumbone

Tetrahydrozerumbone (1·1 g) in ether (20 ml) was reduced with a slurry of 100 mg of lithium aluminium hydride in 20 ml of ether, in a manner detailed above for zerumbone. The product was obtained as a colourless, very viscous liquid, b.p. 123–124°/0·5 mm, n_D^{25} 1·4990. (Found: C, 80·0; H, 12·5. $C_{15}H_{28}O$ requires: C, 80·3; H, 12·6%). The crude 3,5-dinitrobenzoate had m.p. 85–95° and further purification showed it to be a mixture of tetrahydrozerumbyl 3,5-dinitrobenzoates (*vide supra*).

Base-catalysed cleavage of zerumbone

To a solution of 1 g of potassium hydroxide in 3 ml of water and 17 ml of aldehyde-free ethanol, zerumbone (1 g) was added, and the mixture heated on a steam-bath for 6 hr under total reflux, in a flask attached to a one-foot Vigreux column carrying a total condensation-type still-head. After the above period, first 5 ml of the distillate were collected and treated with 2,4-dinitrophenylhydrazine sulphate reagent to give an orange-yellow precipitate (m.p. 95–100°), which was thrice recrystallized from dil alcohol to furnish orange-yellow needles, m.p. 113–114°, mixed m.p. with an authentic sample of methyl ethyl ketone 2,4-dinitrophenylhydrazone (m.p. 113–114°) was undepressed (Found: N, 22·00, 22·10. $C_{10}H_{12}O_4N_4$ requires: N, 22·22%).

Hexahydrozerumbones

Tetrahydrozerumbone (16·65 g, 0·075 mole) was further hydrogenated over 300 mg of pre-reduced PtO_2 catalyst in 75 ml of gl acetic acid. The absorption of hydrogen ceased after 12 hr, when 1990 ml of the gas at 25°/684 mm had been consumed (Calc. for 1 mole of hydrogen: 2030 ml). The catalyst was removed and the filtrate diluted with water (150 ml), extracted with pet ether (20 ml × 3), washed with brine and dried (sodium sulphate). Removal of the solvent gave a mixture of crystals and an oil, which was recrystallized as such from dil alcohol at —10° to give crystals (11 g), m.p. 50–54°. This on two further recrystallizations at —15° from pet ether gave white needles, m.p. 62·5–63°, yield 4·8 g; no colour with tetranitromethane. (Found: C, 80·5; H, 12·5. $C_{15}H_{28}O$ requires: C, 80·3; H, 12·6%). The mother liquors were worked up to give a mixture of stereoisomers, as a colourless liquid, b.p. 115–116°/1 mm, n_D^{24} 1·4820, yield 10·5 g; this was not studied further.

The *oxime* (crude, m.p. 106–107°) was crystallized from dil alcohol to give long, flat needles, m.p. 107–107·5°. (Found: N, 6·1. $C_{15}H_{29}ON$ requires: N, 5·9%). The *semicarbazone* (crude,

m.p. 178–180°) separated from dil alcohol in white needles, m.p. 182–182·5° with effervescence. (Found: N, 15·0. $C_{16}H_{21}ON_3$ requires: N, 14·9%). 2,4-Dinitrophenylhydrazone could not be prepared.

Deoxyhexahydrozerumbone

A mixture of pure hexahydrozerumbone (0·7 g), amalgamated zinc wool (prepared from 3·6 g of zinc and 0·3 g of mercuric chloride in the presence of HCl), acetic acid (3·6 ml) and conc HCl (12·4 ml) was gently refluxed for 15 hr. The refluxing was continued for another 5 hr after adding 5 ml HCl. The reaction mixture was cooled, diluted with water (20 ml) and the hydrocarbon taken up in pet ether (10 ml × 3), the extracts washed with brine and dried. Removal of the solvent, followed by fractionation over sodium gave the desired product as a colourless liquid with properties recorded in Table 2; no colour with tetranitromethane. (Found: C, 85·9; H, 14·1. $C_{15}H_{30}$ requires: C, 85·7; H, 14·3%).

Humulane

A 2·04 g sample of humulene (b.p. 114–115°/5 mm, n_D^{25} 1·5015, $[\alpha]_D^{\pm}$ −1·0) isolated from the essential oil of wild ginger[4,17C] was hydrogenated in 1 g acetic acid over Adam's catalyst when 98·9% of the theoretical quantity of hydrogen was absorbed at room temp and pressure. The reaction mixture was worked up to give 1·2 g of humulane of characteristics given in Table 2; no colour with tetranitromethane.

Ozonolysis of zerumbol

A solution of 2·2 g of zerumbol in purified ethyl acetate (100 ml) was ozonised at −20° with a current of ozonized oxygen (15 mg/min) till no more of ozone was absorbed (2 hr; potassium iodide–boric acid test). The solvent was removed under suction at room temp and the residual colourless syrup taken up in 20 ml of acetic acid. After adding 15 ml of 20% hydrogen peroxide, the clear mixture was heated over the steam-bath for 3 hr and then left aside at room temp overnight. The aqueous acetic acid was removed from a steam-bath/suction and the residue treated with a saturated aqueous sodium bicarbonate solution till alkaline. This was washed with ether to remove a negligible amount of neutral material. The alkaline solution was acidified with conc phosphoric acid and after saturating with ammonium sulphate, was continuously extracted with ether for 24 hr. The solvent was removed to give 1·8 g of a syrup which partially crystallised. This was taken up in carbon tetrachloride (10 ml) and ethanol (5 ml), and after adding 200 mg of sulphosalicylic acid, was gently refluxed in an apparatus permitting continuous removal of the azeotrope. When no more of the lighter phase separated, the product was worked up into sodium bicarbonate soluble (400 mg; half ester of *gem*-dimethylsuccinic acid, *vide infra*) and insoluble portion (1·6 g). The neutral product was further separated by Girard P reagent into a reactive (0·6 g) and non-reactive fraction (0·6 g). The Girard P reactive portion gave a positive test for iodoform and was converted into its 2:4-dinitrophenylhydrazone which after three crystallizations from dil alcohol was obtained in soft, yellow needles (500 mg), m.p. 100–101°, mixed m.p. with an authentic sample of *2:4-dinitrophenylhydrazone of ethyl laevulinate* (m.p. 100–101°) was undepressed. (Found: N, 17·7. $C_{13}H_{16}O_6N_4$ requires: N, 17·3%).

The acidic material (400 mg) was mixed with the Girard P non-reactive fraction and hydrolysed by heating with conc HCl (15 ml) on the steam-bath for 8 hr. Removal of the aqueous acid gave a crystalline residue (0·75 g, m.p. 125–130°), which was thrice recrystallized from acetone–benzene to give prisms (250 mg), m.p. 136–137°, mixed m.p. with a genuine sample of gem-*dimethylsuccinic acid* (m.p. 140–141°) was 137–139°. (Found: C, 49·2; H, 6·9. $C_6H_{10}O_4$ requires: C, 49·3; H, 6·9%).

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STEREOCHEMICAL RELATIONSHIPS IN THE EUDESMANE (SELINANE) GROUP OF SESQUITERPENES

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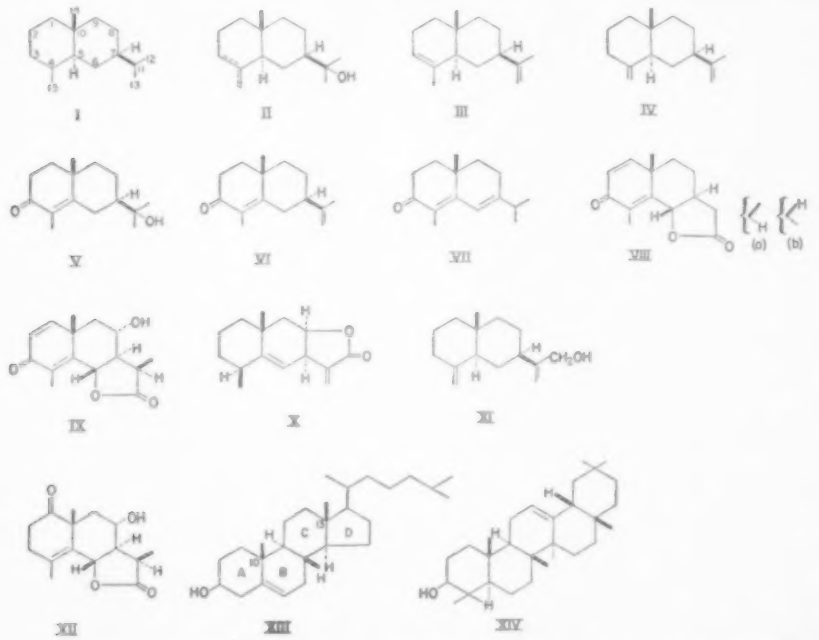
Abstract—The stereochemical correlations in the eudesmane* group of sesquiterpenes are highly ramified. In this article we attempt to summarise the evidence on which the correlations are founded. Most of the classical chemistry of the group of compounds has been reviewed,[1] and some of the more recent developments have been described by Barton and de Mayo.[2]

EUDESMANE has the structure shown in I,[3] and it possesses asymmetric centres at C_4, C_5, C_7 and C_{10}. It is not a naturally occurring compound, but is the parent of a large number of naturally occurring alcohols, ketones, acids and lactones. Introduction of these groups into the parent molecule frequently creates new asymmetric centres,



* For other schemes of nomenclature used in this series see the articles by Kovacs, Herout, Horák, and Šorm, (*Coll. Czech. Chem. Comm.* **21**, 225 ((1956) and Dauben and Hance (*J. Amer. Chem. Soc.* **75**, 3352 (1953)).

[1] (a) Sir John Simonsen and D. H. R. Barton, *The Terpenes* Vol. III, Cambridge Univ. Press (1952); (b) D. H. R. Barton, *Chemistry of Carbon Compounds* (Edited by Rodd) Vol. IIb, p. 630. Elsevier, Amsterdam (1953); (c) A. J. Haagen-Smit, *Fortschr. Chem. Org. Naturstoffe*, **12**, 1 (1955).

[2] D. H. R. Barton and P. de Mayo, *Quart. Rev.* **11**, 189 (1957).

[3] W. Cocker and R. S. Cahn, *Chem. & Ind.* 384 (1955).

particularly at C_6, C_8 and C_{11}. We might mention the following eudesmane derivatives; eudesmol, (II), α- and β-selinenes (III, IV), carissone (V), α-, and β-cyperones (VI, VII), santonin (VIIIa) and 11β (H)-santonin (VIIIb), artemisin (IX), alantolactone (X), sesquibenihiol (XI), and ψ-santonin (XII).

The most important of these asymmetric centres is at C_{10}, comparable with the asymmetric centre at C_{10} in the steroids, e.g. cholesterol (XIII), or triterpenes, e.g. β-amyrin (XIV). It will be shown that without exception all the naturally occurring sesquiterpenes with a eudesmane skeleton, whose stereochemistry is known, possess a 10β-methyl group. In other words the configuration of the 10-methyl group in the 'eudesmanes' and the steroids is identical. As this configuration at C_{10} in the steroids is absolute, it follows that the configuration at C_{10} in the sesquiterpenes is also absolute. It is therefore logical first to trace the relationships at C_{10} of the sesquiterpenoids of the eudesmane type.

It is important to distinguish between the various available proofs of a particular configuration. The least rigorous approach is by analogy; it cannot be termed a proof, although it may provide a good working hypothesis. As an example of this point we can mention the fact that whilst all the known eudesmanes have the 'natural' configuration at C_{10}, the isolation of the 'unnatural' sesquiterpenes of the iresin type,[4] eperuic acid,[5] and cafestol[6] casts some doubt on the universal truth of the hypothesis, even in the eudesmane group. Reasoning by analogy can be applied to asymmetric centres other than C_{10}. It consists in the interpretation of the reactions of the centre in terms of a particular stereochemical configuration. This approach has been greatly facilitated by the development of conformational analysis,[7] and in many cases provides as rigorous a proof as is possible. The use of molecular rotational differences[8] is of considerable importance in the assignment of configuration, and the extension of the method to rotatory dispersion studies[9] has made the method even more valuable. It may be assumed that a rigorous proof of configuration is provided by the method. In the final analysis however a chemical correlation of a compound of unknown configuration with a compound of known configuration provides the ultimate proof.

Configuration at C_{10}

Eudesmol (II). The methyl groups at C_{10} and C_{13} in the steroids are known to be β-orientated.[10] The synthesis[11] of cholesterol (XIII) following essentially the route of the Harvard group of workers uses the laevorotatory unsaturated *trans* decalone (XV) to form rings C and D of the steroid. The angular methyl group in XV therefore

[4] C. Djerassi and S. Burstein, *J. Amer. Chem. Soc.* **80**, 2593 (1958); M. G. Rossmann and W. N. Lipscomb, *Tetrahedron* **4**, 275 (1958); P. Crabbé, S. Burstein, and C. Djerassi, *Bull. Soc. Chim. Belg.* **67**, 632 (1958); L. Caglioti, H. Naef, D. Arigoni, and O. Jeger, *Helv. Chim. Acta* **41**, 2278 (1958).

[5] F. E. King and G. Jones, *J. Chem. Soc.* 658 (1955); J. D. Cocker and T. G. Halsall, *Ibid.* 4262 (1956); C. Djerassi and D. Marshall, *Tetrahedron* **1**, 238 (1957).

[6] H. Bendas and C. Djerassi, *Chem. & Ind.* 1481 (1955); C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **80**, 247 (1958).

[7] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 44 (1956).

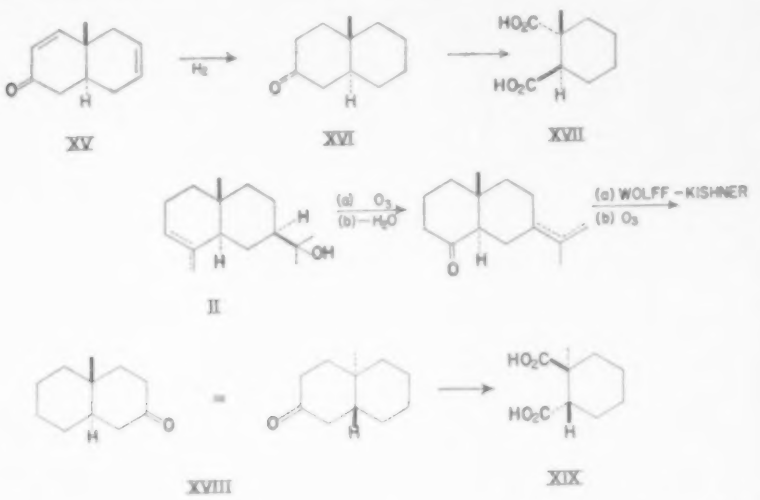
[8] cf. J. A. Mills and W. Klyne, *Progress in Stereochemistry* Vol. I, p. 209. Butterworths, London (1954), where many references are given.

[9] C. Djerassi, E. W. Foltz and A. E. Lippman, *J. Amer. Chem. Soc.* **77**, 4354 (1955); and subsequent papers.

[10] cf. C. W. Shoppee, *Chemistry of the Steroids* p. 23. Butterworths, London (1958).

[11] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.* **74**, 4223 (1952); L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, *Ibid.* **76**, 5014 (1954).

corresponds to that at C_{13} in cholesterol and is consequently β-orientated. Reduction of XV affords the saturated ketone (XVI) which on oxidation is converted to the dicarboxylic acid (XVII), and nothing in these reactions can alter the β-orientation of the angular methyl group. With the absolute configuration of these compounds established it is possible to establish the configuration at C_{10} in eudesmol (II), which is converted[12] by the route shown below to the enantiomorphic forms XVIII and XIX of the decalone (XVI) and its related dicarboxylic acid (XVII).



XV XVI XVII

II

XVIII XIX

These experiments make it clear that eudesmol (II) has the 10β-configuration, and consequently the α- and β-selinenes (III) and (IV) respectively, which are closely related to eudesmol, must also have the β-methyl group at C_{10}.

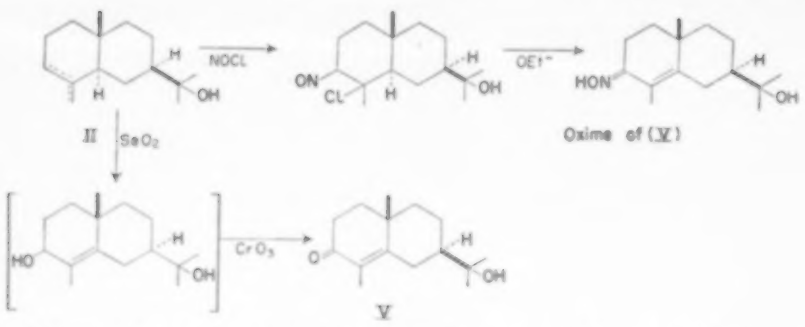
Eudesmol may be considered to be a relay in the correlation of the eudesmane group of sesquiterpenoids with the steroids.

Carissone (V) *and the cyperones* (VI, VII). Carissone (V) has been related[13] to eudesmol (II) and the cyperones (VI, VII) have been related[14] to carissone, by reactions not involving C_{10}. All these compounds thus have the same configuration at C_{10}.

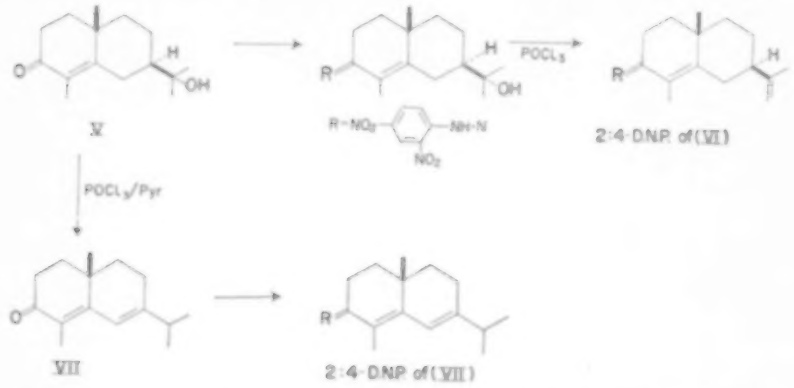
When eudesmol (II) was reacted[13] with nitrosylchloride and the nitroso chloride dehydrochlorinated with sodium ethoxide the oxime of carissone (V) was obtained, but as an oil. Conversion of the oxime to the corresponding 2:4-dinitrophenylhydrazone however gave a crystalline product identical with carissone 2:4-dinitrophenylhydrazone, from which carissone was obtained by reaction with pyruvic acid. Carissone itself was obtained[13] when eudesmol was submitted to successive oxidations with selenium dioxide and chromium trioxide as shown in the reaction sequence below.

Further it has been shown[14] that carissone (V) can be dehydrated, according to the conditions of the reaction, to give either α-cyperone (VI) or β-cyperone (VII), in this way affording a direct correlation between the three ketones. Thus whilst the 2:4-dinitrophenylhydrazone of carissone is dehydrated with phosphorus oxychloride

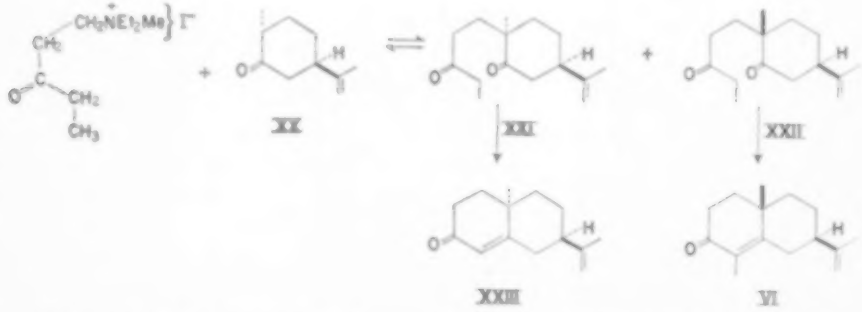
[12] B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold, and R. B. Woodward, *J. Amer. Chem. Soc.* **76**, 313 (1954).
[13] W. A. Ayer and W. I. Taylor, *J. Chem. Soc.* 3027 (1955).
[14] D. H. R. Barton and E. J. Tarlton, *J. Chem. Soc.* 3492 (1954).



and pyridine to give the 2:4-dinitrophenylhydrazone of α-cyperone (VI), dehydration of carissone itself gives β-cyperone (VII), identified as its 2:4-dinitrophenylhydrazone.



The assignment of the configuration shown to α-cyperone (VI) was confirmed by its synthesis[15] in the dextrorotatory form from (+)-dihydrocarvone (XX), whose absolute configuration has been established.[16,17] The reactions afford a good example of stereospecific synthesis.



Two products arise from the condensation of dihydrocarvone with 1-diethylamino-pentan-3-one methiodide, namely, natural (+)α-cyperone (VI) and its stereoisomer

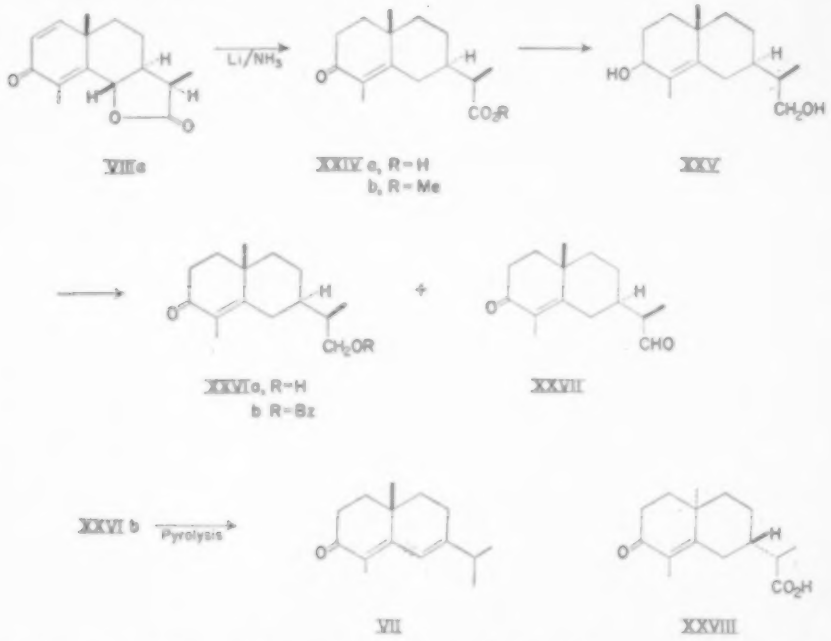
[15] R. Howe and F. J. McQuillin, *J. Chem. Soc.* 2423 (1955).
[16] W. Hückel, *J. Prakt. Chem.* **157**, 225 (1941).
[17] N. L. McNiven and J. Read, *J. Chem. Soc.* 159 (1952).

(XXIII). Of the two intermediate diketones XXI and XXII the former would, on conformational grounds, be expected to be produced the more rapidly, but XXII is thermodynamically more stable than XXI.[18] The formation of XXII, the precursor of natural (+)α-cyperone (VI) undoubtedly arises from a slow equilibration reaction.

It will be noticed that the synthesis also establishes the absolute configuration at C_7 in α-cyperone.

The optical rotatory dispersion curves of carissone and α-cyperone are closely similar to that of 4-methylcholest-4-en-3-one,[19] which confirms the C_{10} configuration shown in (V) and (VI). Synthetic ketones with 7α-(*axial*)-isopropylidene or isopropyl groups show different dispersion curves. As would be expected the dispersion curve of β-cyperone (VII) is similar to that of cholesta-4:6-dien-3-one.

Santonin (VIIIa) *and* 11β(H)-*santonin* (VIIIb). We need not detail here the evidence which demonstrates that these two compounds differ only in configuration at C_{11}. The evidence is given on p. 196. The establishment by chemical methods of the β-methyl configuration at C_{10} in these naturally occurring santonins depends upon the conversion[20] of santonin (VIIIa) to β-cyperone (VII), by the elegant method shown in formulae below.



VIIIa XXIV a, R=H b, R=Me XXV

XXVI a, R=H b R=Bz XXVII

VII XXVIII

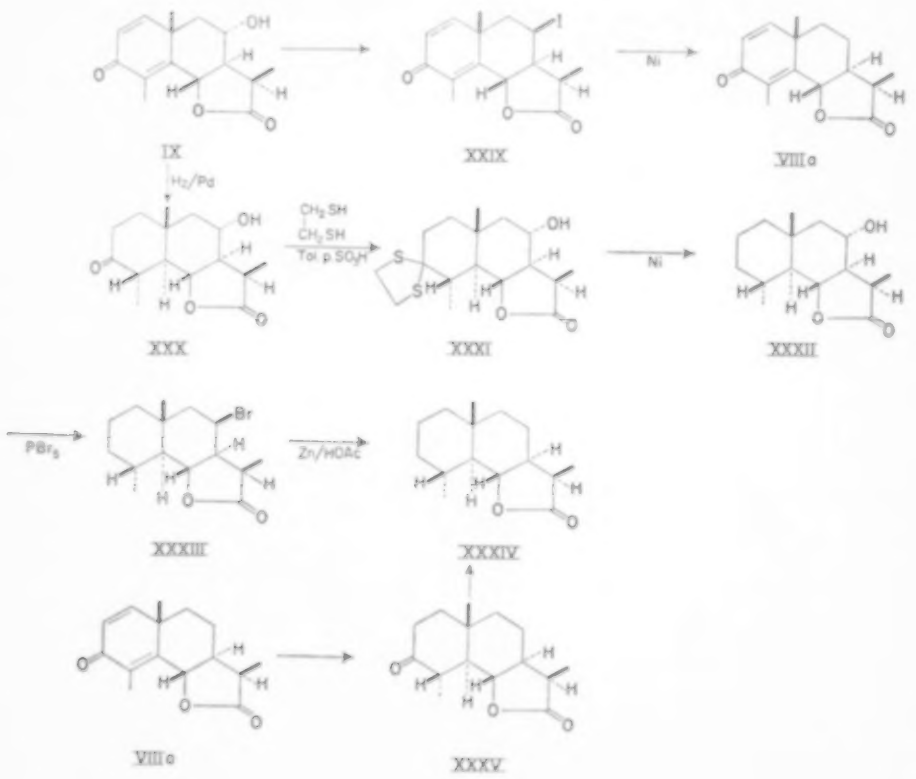
Reduction of santonin (VIIIa) with lithium in liquid ammonia affords the acid (XXIVa). The corresponding ester (XXIVb), when reduced in a mixture of dioxan and ether with lithium aluminium hydride gives the diol (XXV), and this diol undergoes allylic oxidation with manganese dioxide thus affording the ketol (XXVIa), the aldehyde (XXVII) also being produced in this reaction. Pyrolysis of the benzoate

[18] F. J. McQuillin, *J. Chem. Soc.* 528 (1955).
[19] C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956); cf. W. Klyne, *J. Chem. Soc.* 3072 (1953).
[20] H. Bruderer, D. Arigoni, and O. Jeger, *Helv. Chim. Acta* **39**, 858 (1956).

(XXVIb) gives β-cyperone (VII) isolated as its 2:4-dinitrophenylhydrazone, but it is probable that α-cyperone (VI) is produced first.

The rotatory dispersion curve of santonin differs sufficiently from that of cholesta-1:4-dien-3-one its closest steroidal analogue to draw any stereochemical conclusion from it.[19] However the acid (XXVIII) used in the synthesis of the antipode of santonin has a dispersion curve which is almost the mirror image of that of carissone (V). Further support for the presence of 10β-methyl group comes from the dispersion curves of the tetrahydrosantonins (p. 202), and molecular rotation data have also been employed to arrive at the same conclusion.[21]

Artemisin (IX). Artemisin has been shown[22] to be 8α-hydroxysantonin (IX). Two routes were employed for the correlation of this compound with santonin (VIIIa). In the first, artemisin was converted to 8-iodosantonin (XXIX) by the use of triphenylphosphite methiodide, and santonin (VIIIa) was then produced when the

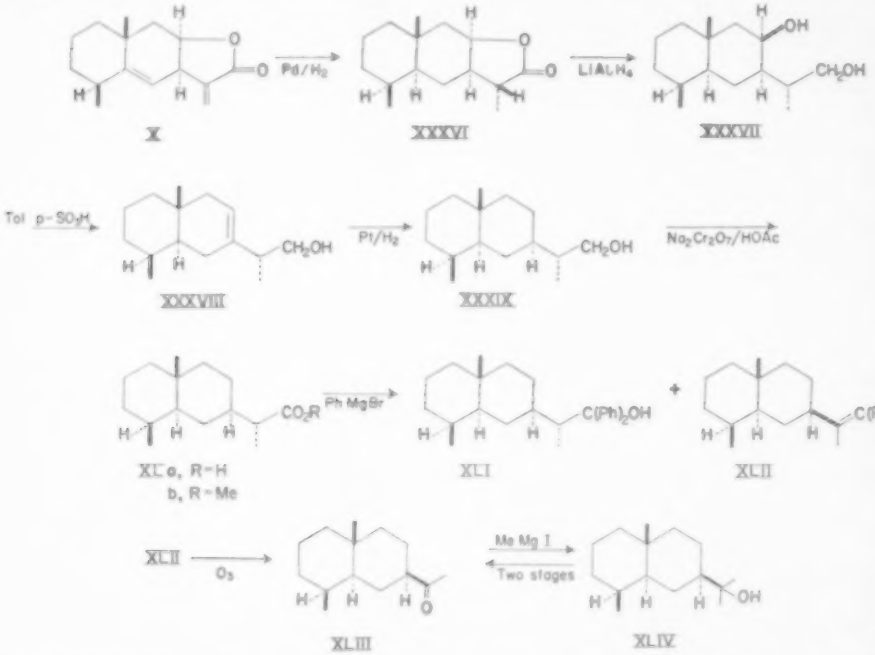


iodo compound was reduced over Raney nickel in pyridine-methanol solution. In the second route artemisin was reduced over palladised charcoal to its tetrahydro compound (XXX), from which the keto group was removed by way of the ethylene

[21] Y. Abe and M. Sumi, *Chem. & Ind.* 253 (1955); E. J. Corey, *J. Amer. Chem. Soc.* **77**, 1044 (1955).
[22] M. Sumi, *Pharm. Bull. Japan* **5**, 187 (1957); *Proc. Japan Acad.* **33**, 153 (1957); *J. Amer. Chem. Soc.* **80** 4869 (1958).

thioketal (XXXI) which was desulphurised with Raney nickel. Treatment of the deoxo compound (XXXII) with phosphorous pentabromide afforded the bromo compound (XXXIII), presumably with inversion at C_8, which on reduction with zinc and acetic acid gave a desoxytetrahydrosantonin, namely 5:11α(H), 4:6β(H)-eudesman-6:13-olide (XXXIV). This lactone was also obtained when 3-oxo-5:11α(H), 4:6β(H)-eudesman-6:13-olide (α-tetrahydrosantonin) (XXXV) was reduced *via* its ethylene thioketal. Since the configuration of α-tetrahydrosantonin (XXXV) is known[23] the configuration of tetrahydroartemisin must be that shown in (XXX).

Alantolactone (X). Alantolactone has been converted[24] to dihydroeudesmol (XLIV) by a method which proves that these compounds have the same configuration both at C_{10} and C_7. It will be noticed that we employ the structure X[25] for alantolactone in preference to the alternative structure in which the endocyclic double bond is in the 3:4-position.[26] The former structure seems to us to be more in accord with degradative evidence than the latter.



Alantolactone (X) is readily reduced to its tetrahydro compound, whose structure has been shown to be XXXVI (see pp. 189, 200). The diol (XXXVII), obtained when tetrahydroalantolactone is reduced with lithium aluminium hydride, is dehydrated with toluene *p*-sulphonic acid thus affording the unsaturated compound (XXXVIII). Reduction of the latter gives the saturated alcohol (XXXIX) which on oxidation with dichromate in acetic acid gives the acid (XLa). The corresponding methyl ester (XLb) reacts with phenylmagnesium bromide giving the alcohol (XLI) and the

[23] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4549 (1956); O. Kovacs, V. Herout, M. Horák and F. Šorm, *Coll. Czech. Chem. Comm.* **21**, 225 (1956); M. Yanagita and A. Tahara, *J. Org. Chem.* **20**, 959 (1955).
[24] K. Tanabe, *Pharm. Bull. Japan* **6**, 214 (1958).
[25] C. Asselineau and S. Bory, *C. R. Acad. Sci., Paris* **246**, 1874 (1958).
[26] K. Tsuda, K. Tanabe, I. Iwai and K. Funakoshi, *J. Amer. Chem. Soc.* **79**, 5721 (1957).

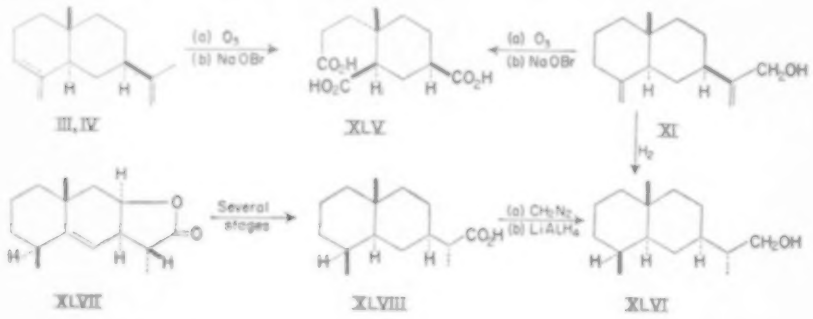
unsaturated compound (XLII). Ozonolysis of the latter compound affords the methyl ketone (XLIII) which may be obtained from dihydroeudesmol (XLIV), and into which it can be converted on reaction with methylmagnesium iodide.

Further evidence of the stereochemistry of alantolactone comes from its correlation with sesquibenihiol (XI).

Sesquibenihiol (*Costol*) (XI). Recent work[27] has shown that sesquibenihiol is identical with costol, an alcohol isolated from *Saussurea Lappa*.

Almost fifty years ago it was shown[28] that the tricarboxylic acid (XLV) could be obtained by the oxidation of the selinenes, and since the configuration of the selinenes is that shown in III and IV (p. 183), the tricarboxylic acid (XLV) must also have the selinene configuration at C_7 and C_{10}. The same acid has more recently[27,29] been obtained by the oxidation of sesquibenihiol (XI). The configuration of the latter at C_7 and C_{10} is consequently the same as that of the selinenes at these centres.

Sesquibenihiol (XI) has also been related[30] to alantolactone (X). Reduction of sesquibenihiol gives a tetrahydro derivative (XLVI)[27,29] which is identical with an alcohol prepared from dihydroalantolactone (XLVII) *via* the acid (XLVIII).

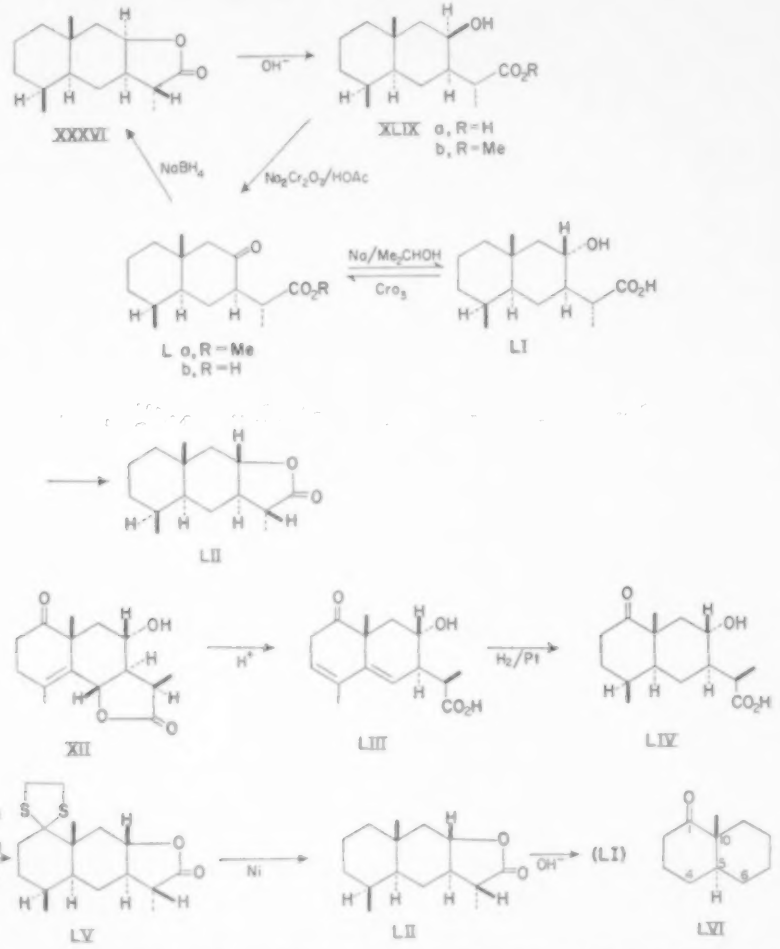


ψ-Santonin (XII). When tetrahydroalantolactone (XXXVI, see pp. 189, 200) is hydrolysed with alkali, and the product carefully neutralised the acid (XLIXa) is obtained, which with diazomethane gives the methyl ester (XLIXb).[26] Oxidation of the ester with dichromate in acetic acid gives the keto ester (La) which is hydrolysed with alkali to the keto acid (Lb). Reduction of the latter with sodium and isopropanol affords the hydroxy-acid (LI), which is lactonised to (LII). On the other hand borohydride reduction of (Lb) gives tetrahydroalantolactone (XXXVI),[26] hence the two lactones XXXVI and LII have opposite configuration at C_8. This will be discussed on p. 195.

The hydroxy-acid (LI) may be obtained from ψ-santonin as follows.[31] ψ-Santonic acid (LIII), an acid catalysed rearrangement product of ψ-santonin,[32] is readily reduced to its tetrahydro derivative (LIV),[32,33] from which the keto group is removed *via* the ethylene thioketal (LV). The desoxy compound (LII) was however produced

[27] V. Benešová, V. Sýkora, V. Herout, and F. Šorm, *Chem. & Ind.* 363 (1958).
[28] F. W. Semmler and F. Risse, *Ber. Dtsch. Chem. Ges.* **46**, 599 (1913).
[29] S. Katsura, *J. Chem. Soc. Japan* **63**, 1460 (1942).
[30] T. Ukita and S. Nakazawa, *Pharm. Bull. Japan* **2**, 239 (1954).
[31] W. Cocker and T. B. H. McMurry, *Proc. Chem. Soc.* 147 (1958).
[32] G. R. Clemo and W. Cocker, *J. Chem. Soc.* 30 (1946); N. M. Chopra, W. Cocker, J. T. Edward, T. B. H. McMurry, and E. R. Stuart, *Ibid.* 1828 (1956).
[33] W. Cocker and C. Lipman, *J. Chem. Soc.* 1170 (1949).

as a gum, but the corresponding acid was obtained as a highly crystalline compound identical with LI. None of these reactions involve C_{10} consequently ψ-santonin and alantolactone have the same β-methyl configuration at this centre.



Comparison of the rotatory dispersion curves[19,34] of tetrahydro-ψ-santonic acid (LIV) and *trans* 10-methyldecal-1-one (LVI) supports the configuration of ψ-santonin. The rotatory dispersion curves of ψ-santonin and ψ-santonic acid cannot supply any information in the absence of suitable model compounds for comparison.

We can now summarise the foregoing correlations in Chart I.

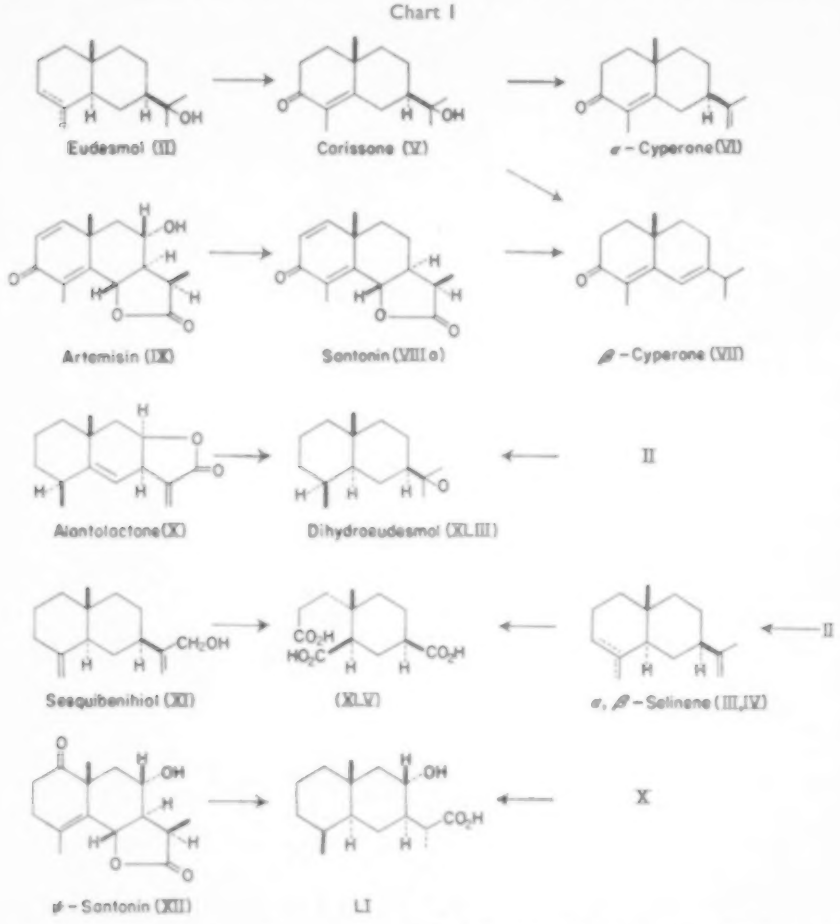
Configuration at C_4

Alantolactone (X). Alantolactone (X) and isoalantolactone (LVII) afford the same tetrahydro derivative XXXVI, which must therefore possess the same configuration at C_4 as alantolactone. This configuration has been established in an ingenious manner. Dihydroisoalantolactone (LVIII) can be converted[35] to its

[34] C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958).

3-hydroxy derivative (LIX) which on hydrogenation gives 3-hydroxytetrahydroalantolactone (LX). Oxidation of the latter with dichromate in acetic acid affords 3-oxotetrahydroalantolactone (LXI) in which the 4-methyl group is axial (β) since this centre

Chart I



undergoes inversion with alkaline alumina[36,cf.23] giving the lactone (LXII) in which the methyl is equatorial (α). Now, when the keto group is removed from the ketolactones LXI and LXII by way of their thioketals the deoxolactones XXXVI, which is tetrahydroalantolactone, and LXIII are respectively obtained. Obviously therefore alantolactone has the axial 4β-methyl group, shown in (X).

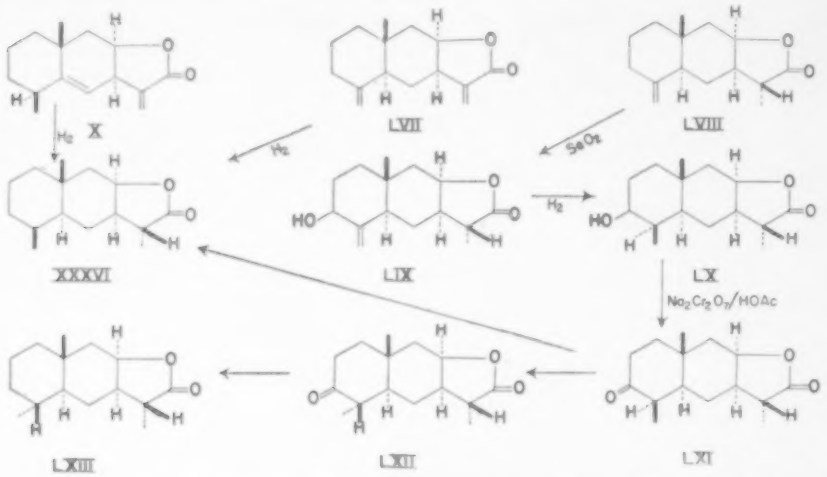
Configuration at C_5

Whilst a number of eudesmanes have an asymmetric centre at C_5, in others this centre becomes of importance after reduction. Of the former type mention can be made of eudesmol (II), the selinenes (III, IV), and sesquibenihiol (XI).

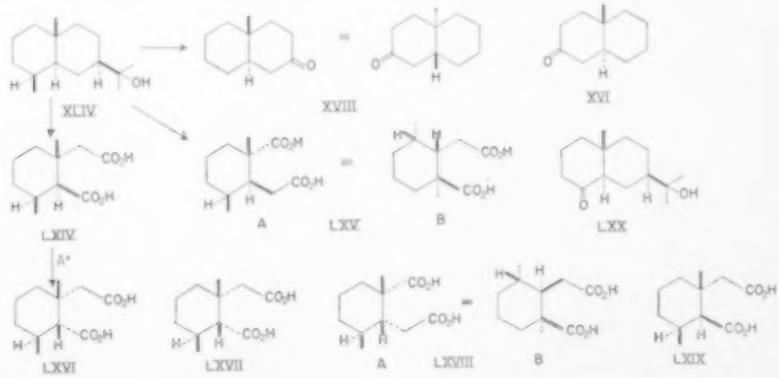
It was shown earlier (p. 183), that eudesmol can be converted to the *trans* decalone

[25] H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan* **74**, 738 (1954).
[26] K. Tanabe, *Pharm. Bull. Japan* **6**, 218 (1958).

(XVIII), the enantiomorph of XVI, a compound of known absolute configuration. It follows from this evidence that eudesmol and hence the selinenes and sesquibenihiol are *trans* decalin derivatives with αH at C_5.



The *trans* ring junction is supported by consideration of the molecular rotations of the dicarboxylic acids (LXIV) and (LXV), oxidation products of dihydroeudesmol,[38] and the acid epimerisation product (LXVI) obtained from LXIV.[39] If the ring junction is *trans*, and we consider the methyl groups and the hydrogen to be equivalent, then obviously LXIV and LXV (written as LXVB) are of the same stereochemical type. As expected on this formulation they have similar positive rotations, whilst LXVI has a negative rotation. If however the ring junction were *cis* then the dicarboxylic acids would be LXVII, LXVIII and LXIX respectively. These formulations cannot be accepted since LXVIII (written as LXVIIIB) is enantiomeric with LXVII and hence these two acids should have rotations of opposite, not the same, sign.



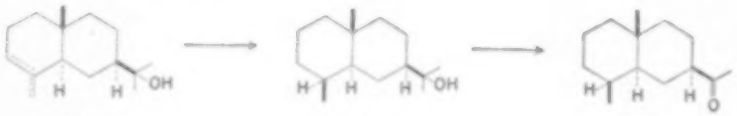
[37] W. Klyne, *J. Chem. Soc.* 3072 (1953).
[38] L. Ruzicka, P. A. Plattner, and A. Fürst, *Helv. Chim. Acta* **25**, 1364 (1942); P. A. Plattner, A. Fürst, and J. Hellerbach, *Ibid.* **30**, 2158 (1947).
[39] D. H. R. Barton, *Chem. & Ind.* 664 (1953); *J. Chem. Soc.* 1027 (1953).

It has also been shown[40] that the ketol (LXX) derived from eudesmol by oxidation is stable to alkali as would be expected of a *trans* A/B ring junction.

Configuration at C_7

In all the eudesmanes where the configuration at C_7 is known, the isopropyl group is β-equatorial.

We have mentioned earlier that dihydroeudesmol (XLIV) is converted in two stages to the ketone (XLIII) which is unaffected by alkali.[12] The isopropyl group must therefore be equatorial, and since the decalin system is *trans* fused the isopropyl group must have also the β-configuration. From the evidence described earlier in this review, it is clear that the selinenes (III, IV), carissone (V), α-cyperone (VI), alantolactone (X), and ψ-santonin (XII), which have been related (Chart I) to eudesmol by reactions not involving C_7, must have the β-(equatorial)-isopropyl group at this centre.



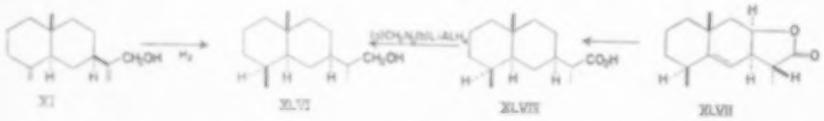
II XLIV XLIII

The configuration at C_7 in alantolactone is confirmed by the stability to alkali of the keto-acid (Lb) and ester (La), obtained[26] from tetrahydroalantolactone (XXXVI).

XXXVI La, R=Me b, R=H

It may be argued that inversion at C_7 could have taken place in the formation of the keto-acid (La) and ester (Lb) from the tetrahydroalantolactone (XXXVI), but this is obviously incorrect since tetrahydroalantolactone is reformed when the keto-acid (Lb) is reduced with sodium borohydride.

The configuration at C_7 of sesquibenihiol (XI) is proved by its reduction to the saturated alcohol[27,39] (XLVI) which may also be obtained from dihydroalantolactone (XLVII). Chart I shows that santonin (VIIIa), and artemisin (IX) have the same



XI XLVI XLVIII XLVII

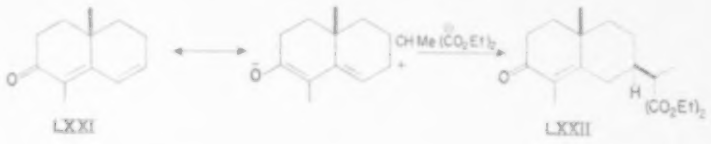
configuration at C_7. Whilst their conversion to β-cyperone (VII) probably proceeds[14] *via* α-cyperone (VI), proof is lacking. However stereospecific synthesis[41] of the

[40] A. J. Birch and K. M. C. Mostyn, *Aust. J. Chem.* **7**, 301 (1954).

[41] Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *Proc. Japan Acad.* **28**, 425 (1952); **29**, 113 (1953); **30**, 116, 119 (1954); *J. Amer. Chem. Soc.* **75**, 2567 (1953); cf. M. Matsui, K. Toki, S. Kitamura, Y. Suzuki, and M. Hamuro, *Bull. Chem. Soc. Japan* **27**, 5 (1954); W. Cocker, *Ann. Rep.* **51**, 208 (1954); W. Cocker and J. T. Edward, *Ibid.* **52**, 191 (1955).

santonins VIIIa and VIIIb makes it clear that these compounds afford no exception to the usual configuration at C_7.

In this synthesis the conjugated unsaturated lactone (LXXI)[42] adds the methylmalonic ester anion so that it takes up the more stable equatorial position,[43] thus affording (LXXII). This is the stage in the synthesis which determines the stereochemistry at C_7 in santonin, and we need not here consider the remainder of the synthesis, which does not further concern this centre.



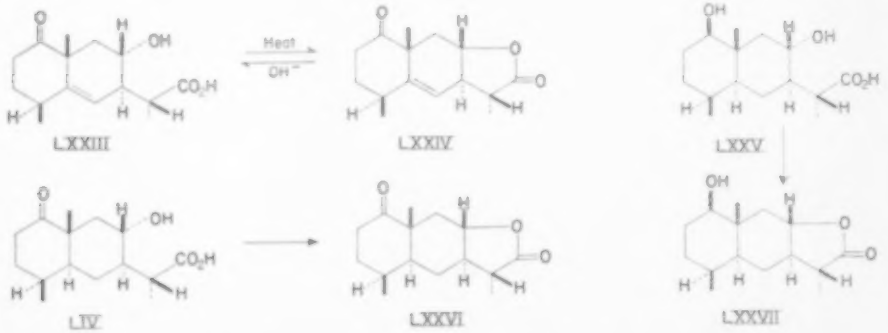
LXXI LXXII

Configuration at C_8

Artemisin (IX), *Alantolactone* (X), *and ψ-Santonin* (XII). In artemisin (IX), and in ψ-santonin (XII), the hydroxyl group at C_8 is α-(equatorial), whilst in alantolactone (X) the lactone ring is β-fused.

Both artemisin[22] and ψ-santonin[44] can be esterified without difficulty, which suggests equatorial hydroxyl. In addition there is a strong positive shift[22] in molecular rotation in proceeding from santonin (VIIIa) to its 8-hydroxy derivative artemisin (IX), and on acetylation of the latter there is a further positive rotational shift. Such shifts indicate[45] α-orientation of the hydroxyl in question.

Further light on the configuration at C_8 in ψ-santonin is thrown by a consideration of the lactonisation of dihydro-ψ-santonin (LXXIII) in which C_8 has the same configuration as its parent. The lactonisation, which affords LXXIV, takes place with considerable negative increment in molecular rotation. Similarly tetrahydro-ψ-santonic acid (LIV) and hexahydro-ψ-santonic acid (LXXV) undergo lactonisation to the anhydro compounds LXXVI and LXXVII respectively with negative incremental changes in molecular rotation.[32]

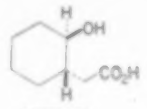


LXXIII LXXIV LXXV

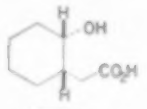
LIV LXXVI LXXVII

[42] F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1437 (1952).
[43] R. B. Woodward and P. Yates, *Chem. & Ind.* 1391 (1954); J. W. Ralls, *J. Amer. Chem. Soc.* **75**, 2123 (1953).
[44] N. M. Chopra, W. Cocker, B. E. Cross, J. T. Edward, D. H. Hayes, and H. P. Hutchison, *J. Chem. Soc.* 588 (1955).
[45] W. Klyne and W. M. Stokes, *J. Chem. Soc.* 1979 (1954); D. H. R. Barton and A. Nickon, *Ibid.* 4665 (1954).
[46] N. M. Chopra, W. Cocker, and J. T. Edward, *Chem. & Ind.* 1535 (1954).

In reinterpreting Hudson's lactone rule, Klyne[47] has shown that in a hydroxy-acid such as (LXXVIII) oriented as shown, lactonisation takes place with positive increment in molecular rotation, and conversely the hydroxy acid (LXXIX) lactonises with negative change in molecular rotation. The ψ-santonin derivatives mentioned above behave in a similar manner to (LXXIX) and hence they have α-hydroxyl at C_8

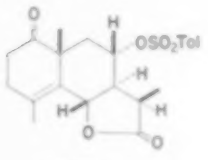


LXXVIII

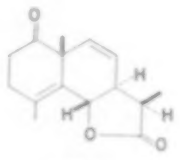


LXXIX

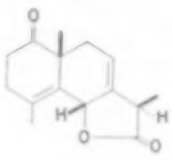
Similar conclusions about the configuration at C_8 in ψ-santonin have been reached by Dauben and Hance,[48] who showed that the tosyl ester of ψ-santonin (LXXX) undergoes ready base catalysed elimination of toluene sulphonic acid to give LXXXI, rather than LXXXII. Since *trans* elimination takes place, it can be assumed that the C_8 tosyloxy group and C_7 hydrogen have *cis* relationship. Consequently the hydroxyl at C_8 is α-orientated, since the C_7 hydrogen is α-orientated (see p. 192).



LXXX

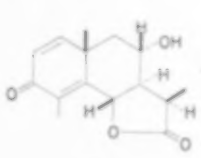


LXXXI

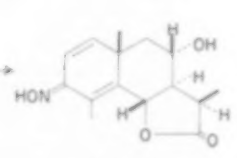


LXXXII

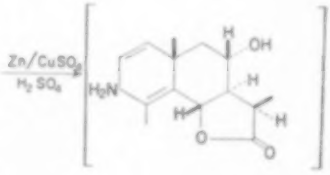
It has also been shown[49] that ψ-santonin (XII) and artemisin (IX) have the same configuration at C_8. Artemisin oxime (LXXXIII) is reduced in acid solution to give the *trans* lactone hypoartemisin (LXXXIV), by a reaction similar to the conversion[50] of santonin to hyposantonin. Hypoartemisin is converted to isohypoartemisin, the *cis* lactone (LXXXV), by hydrolysis with alkali and acidification of the sodium salt. This is analogous to the conversion of hypo- to isohyposantonin.[50] The *cis* lactones

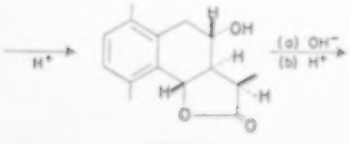


IX

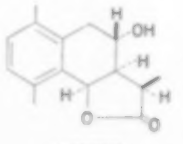


LXXXIII

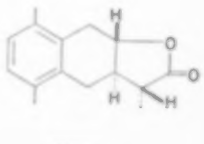




LXXXIV



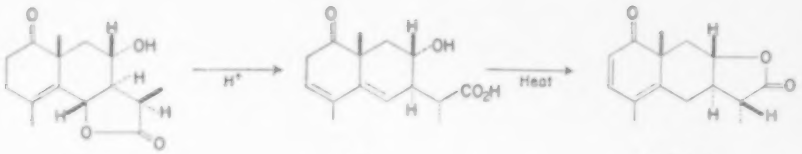
LXXXV



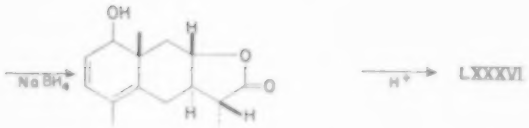
LXXXVI

[47] W. Klyne, *Chem. & Ind.* 1198 (1954).
[48] W. G. Dauben and P. D. Hance, *J. Amer. Chem. Soc.* **77**, 606 (1955).
[49] M. Sumi, W. G. Dauben, and W. K. Hayes, *J. Amer. Chem. Soc.* **80**, 5704 (1958).
[50] Ref. 1a, p. 252.

(but not the *trans*) are reduced with zinc and acetic acid, giving in the case of isohypoartemisin, the linear lactone (LXXXVI). The same lactone was obtained[51] from ψ-santonin (XII) *via* ψ-santonic acid (LIII) and its anhydro compound (LXXXVII).[32,52]



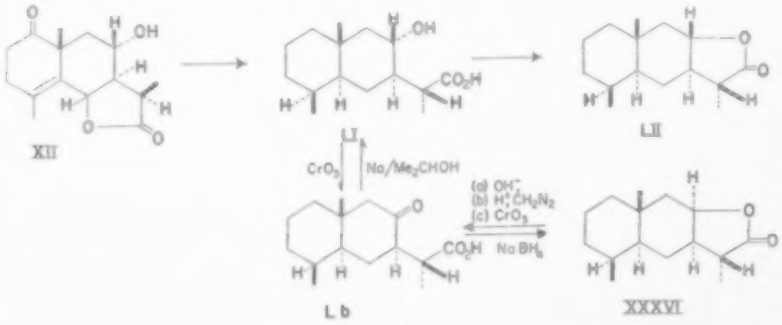
XII LIII LXXXVII



LXXXVI

These investigations[49] carried out by Dauben and his co-workers establish the fact that artemisin and ψ-santonin have the same configuration not only at C_8, but also at C_7 and C_{11}.

We have shown earlier (p. 188) that ψ-santonin (XII) has been related[31] to alantolactone (X). We pointed out that ψ-santonin may be converted to the hydroxy-acid (LI), and its lactone (LII), which compounds may also be obtained[26] from tetrahydroalantolactone (XXXVI). The hydroxy acid corresponding to (XXXVI) is oxidised to the keto-acid (Lb), which on reduction with sodium and isopropanol on the one hand affords the hydroxy-acid (LI), whilst on the other hand reduction with sodium borohydride regenerates tetrahydroalantolactone (XXXVI). Since the hydroxy acid (LI) may be reoxidised[53] to the keto-acid (Lb), it is clear that the two lactones XXXVI and LII differ only in configuration at C_8.



XII LII

Lb XXXVI

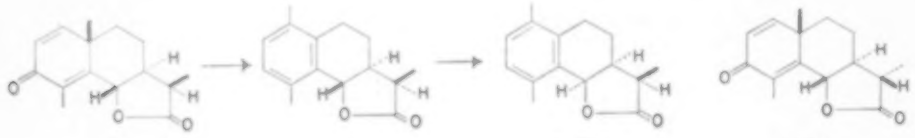
Reduction of a ketone with sodium in an alcohol affords equatorial hydroxyl. The hydroxy-acid (LI) must therefore have α-(equatorial) hydroxyl at C_8, and the lactone LII must consequently be *trans* fused. Sodium borohydride however usually

[51] W. G. Dauben, P. D. Hance, and W. K. Hayes, *J. Amer. Chem. Soc.* **77**, 4609 (1955).
[52] W. Cocker, B. E. Cross, and C. Lipman, *J. Chem. Soc.* 959 (1949).
[53] W. Cocker, T. B. H. McMurry and L. O. Hopkins, *J. Chem.* 1998 (1959).

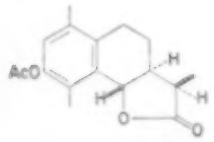
affords axial hydroxyl when the keto group, as in Lb, is hindered. Hence the hydroxy-acid corresponding to tetrahydroalantolactone XXXVI must have β-(axial) hydroxyl at C_8, and tetrahydroalantolactone is thus a *cis* fused lactone.

Configuration at C_{11}

Santonin (VIIIa) *and* 11β(H)-*santonin* (VIIIb). The two santonins mentioned are *trans* fused lactones. This is shown by the fact that santonin may be converted[50] by a series of reactions not involving C_6, to hyposantonin (LXXXVIII), which must have the same lactone ring system as santonin. Gentle alkaline hydrolysis of hyposantonin and acidification of the product however affords a more stable lactone isohyposantonin (LXXXIX), which must therefore be *cis* fused. Epimerisation at C_6 takes place when the sodium salt produced by hydrolysis, is acidified. Again when santonin (VIIIa) is treated[54] under very mild conditions with a mixture of acetic anhydride and acetyl chloride, which cannot affect the lactone ring it affords the acetate of a *trans* fused desmotroposantonin (XC).



VIIIa LXXXVIII LXXXIX VIIIb



XC

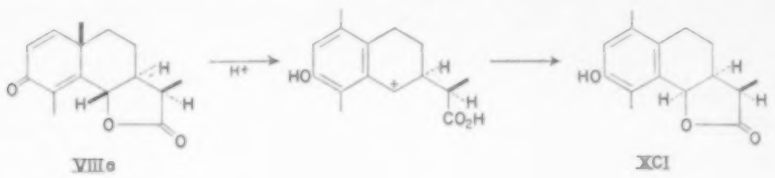
Treatment of santonin (VIIIa) with cold dilute sulphuric acid affords the so-called (−)α-desmotroposantonin (XCI), which is also obtained as its acetate when the acetate (XC) is treated with acid. The only logical deduction from the latter reaction is that (−)α-desmotroposantonin (XCI) is a *cis* fused lactone.[55]

If we accept this view, then in XCI the β-methyl group at C_{11} interacts with the CH_2 at C_8 to a greater degree than its C_{11} epimer, and is thus thermodynamically in the less stable of the two configurations. It can assume the more stable configuration by one of two ways. Either C_{11} can be epimerised leaving C_6 and C_7 unaffected or these centres can be epimerised leaving C_{11} unaffected. In fact when (−)α-desmotroposantonin (XCI) is treated with warm dilute sulphuric acid it undergoes inversion at C_6 and C_7[55] giving (+)β-desmotroposantonin (XCII), in which C_{11} has the more stable configuration.

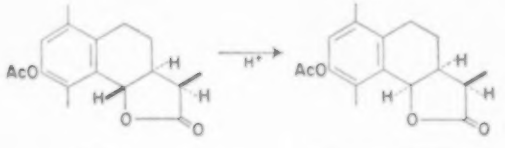
Now when (+)β-desmotroposantonin (XCII) is fused with potassium hydroxide it gives (+)α-desmotroposantonin (XCIII), the enantiomorph of XCI. This change seems to be thermodynamically impossible for in (+)α-desmotroposantonin (XCIII)

[54] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4430 (1955).
[55] Ref. 1(a), pp. 263–269; Huang-Minlon, *J. Amer. Chem. Soc.* **70**, 610 (1948); D. H. R. Barton, *J. Org. Chem.* **15**, 466 (1950).

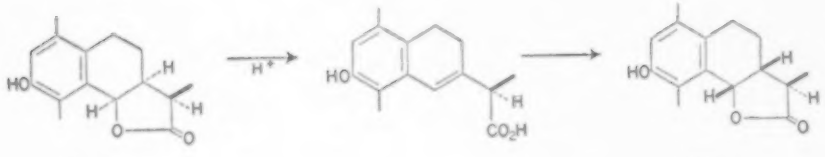
the methyl group at C_{11} again interacts with the CH_2 at C_8. However it should be remembered[43,56] that during the potash treatment the ion XCIV is present and it is this which undergoes inversion at C_{11} to the more stable ion XCV. Cyclisation of the latter will then afford (+)α-desmotroposantonin (XCIII).



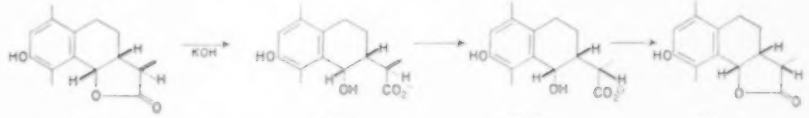
VIIIa XCI



XC Acetate of (XCI)

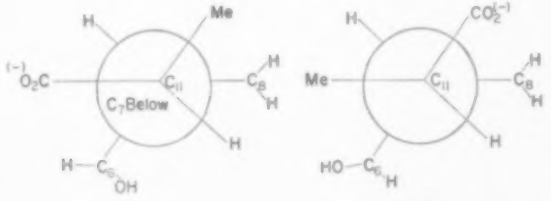


XCI XCII



XCII XCIV XCV XCIII

That XCV is the more stable ion is seen in the diagrams below which show that in XCV the CO_2^- group is maximally removed from C_6, the largest group on C_7.



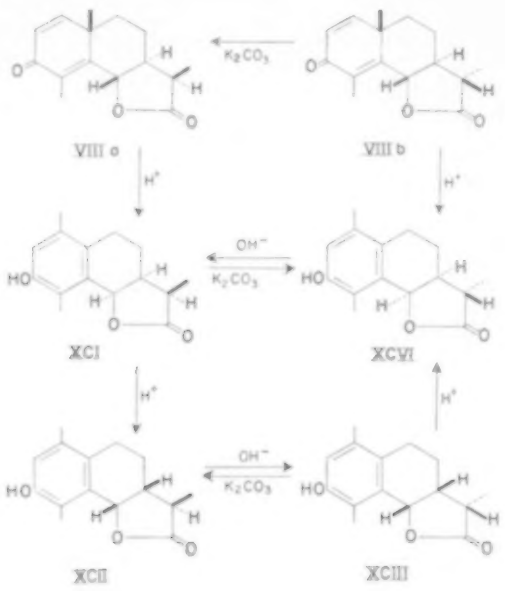
XCIV XCV

The fact that (+)α-desmotroposantonin XCIII has the more unstable of the two possible configurations at C_{11} is shown as follows: (a) when it is heated with anhydrous potassium carbonate in xylene,[56] under which conditions the lactone remains intact, it affords (+)β-desmotroposantonin (XCII) by epimerisation at C_{11}

[56] N. M. Chopra, W. Cocker, and J. T. Edward, *Chem. & Ind.* 41 (1955).

via the enol, and (b) it affords (—)β-desmotroposantonin (XCVI) when heated with dilute sulphuric acid. Finally, to complete the picture (—)β-desmotroposantonin (XCVI) is (a) obtained from 11β(H)-santonin (VIIIb) with cold dilute acid, (b) is obtained when (—)-α-desmotroposantonin (XCI) is heated with potassium carbonate[56] and (c), it affords (—)α-desmotroposantonin (XCI) when heated with potash.

The full cycle of reactions is shown below and they make it clear that santonin (VIIIa) and 11β(H)-santonin (VIIIb) differ only in configuration at C_{11} and that the former has β-methyl at this centre.



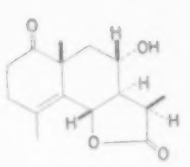
Models show that in both santonin and 11β(H)-santonin, whilst there is no direct interaction between the 11-methyl group and the 8-methylene group, there is greater interference between the 11α-methyl and the lactone carbonyl group than there is in the C_{11} epimer.[54] Hence 11β(H)-santonin has the more unstable lactone. This has been verified experimentally for on heating with anhydrous potassium carbonate,[54] 11β(H)-santonin can be converted to santonin.

Gathering up the above experimental facts it seems clear that (a) with a *cis* fused butanolide the more stable configuration is the one in which the 11-methyl group is *cis* to the 7-hydrogen atom, and (b) with a *trans* fused butanolide the more stable configuration is the one in which the 11-methyl group is *trans* to the 7-hydrogen atom. Corollaries to these rules are (c) when two *cis* fused butanolides are possible, that in which the 11-methyl group is *cis* to the 7-hydrogen atom will be preferred; and (d) when two *trans* fused butanolides are possible that in which the 11-methyl group is *trans* to the 7-hydrogen atom will be preferred (cf. ψ-santonin below).

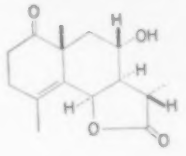
In contrast to the views given above santonin and 11β(H)-santonin have been assigned the opposite configuration at C_{11},[56] but the arguments advanced in support of the hypothesis are dubious. In particular the changed configurations do not explain the reactions of the desmotroposantonins (see p. 196).

Artemisin (IX). We have shown earlier (Chart I) that artemisin is 8-hydroxysantonin. Consequently artemisin has the 11β-methyl group.

ψ-*Santonin* (XII). We have assigned the 11β-methyl configuration to ψ-santonin,[32] on the following evidence. ψ-Santonin is stable to anhydrous potassium carbonate in boiling xylene and therefore it has the more stable configuration at C_{11}. We can therefore write ψ-santonin as either XII or XCVII, using the rules propounded above.

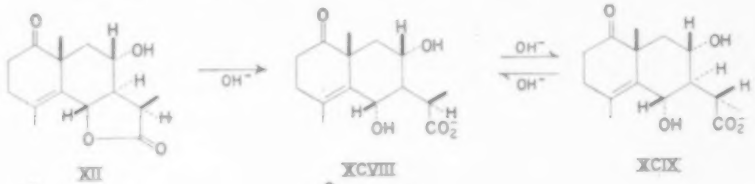


XII

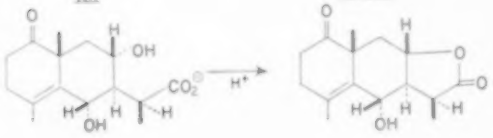


XCVII

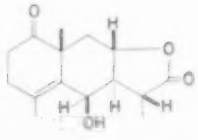
Now when ψ-santonin is heated with potassium hydroxide it gives iso-ψ-santonin,[32] which does not differ from ψ-santonin in its functional groups. On the basis of the preferred structure XII, because of its relationship to santonin, ψ-santonin would be expected with alkali to give the ion XCVIII, which would epimerise at C_{11}[56] to give XCIX, or at least equilibrate with it. On acidification the latter ion would ring-close with the C_8 hydroxyl to give the linear iso-ψ-santonin (C).



XII XCVIII XCIX



C



CI

iso-ψ-Santonin is however stable to potassium carbonate and this is in agreement with the formulation of the lactone as C, which from the rules mentioned above, would be expected to be more stable than its C_{11} epimer. The alternative formulation for ψ-santonin, namely XCVII would lead to the unstable linear iso-ψ-santonin (CI).

Finally as we have already indicated (p. 194), ψ-santonin has been related[49] to artemisin by methods not involving C_{11}, thus showing that ψ-santonin (XII) has the same β-methyl configuration at C_{11} as artemisin, and hence the same as santonin (VIIIa).

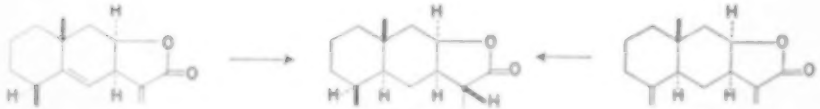
Configuration at C_6 in the lactones

The santonins (VIIIa,b) *artemisin* (IX), *ψ-santonin* (XII). The santonins mentioned have *trans* fused lactone rings; the evidence for this has already been discussed (p. 196). This requirement and the β-orientation of the isopropyl residue at C_7 (p. 192) implies α-linkage of the lactone at C_6. The conversion of artemisin (IX) to santonin without affecting C_6 also implies α-lactone ring fusion in artemisin. Likewise from our discussion of the stereochemistry at C_{11} in ψ-santonin (XII, p. 199) this lactone must also have similar stereochemistry at C_6 to that of the other lactones mentioned.

Stereochemistry of the reduced eudesmanes

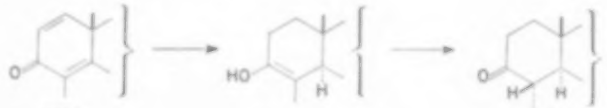
Catalytic reduction of the unsaturated derivatives of eudesmane takes place so that hydrogen adds to the less hindered α-face of the molecule. This is seen in the hydrogenation of eudesmol (II) to give dihydroeudesmol (XLIV), and of both alantolactone (X) and isoalantolactone (LVII) to give tetrahydroalantolactone (XXXVI).

II XLIV



X XXXVI LVII

In cases where there is a 4-en-3-one system as in α-cyperone (VI), santonin (VIIIa), 11β(H)-santonin (VIIIb), and artemisin (IX), the position is complicated by the fact that addition can take place either across the 4:5-double bond, or at the ends of the 4-en-3-one system as a whole. In the latter case the intermediate enol (CII) can rearrange to the stable 4β:5α(H)-system (CIII).



VIII a CII CIII

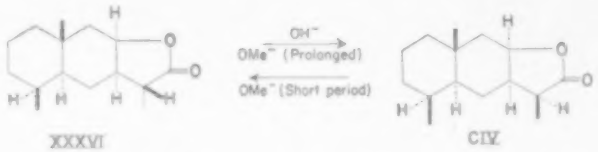
1:2 Addition is favoured in non-polar solvents and 1:4-additions in highly polar solvents as noted in the steroid field.[11]

It has been assumed for some time,[39] that dihydroeudesmol could be represented as XLIV. This has recently[58] been proved, by the conversion of tetrahydroalantolactone (XXXVI)[36] whose configuration at C_4 has already been proved (see p. 189), to dihydroeudesmol by reactions not involving C_4. It is clear from these reactions

[57] Y. Abe, T. Miki, M. Sumi, and T. Toga, *Chem. & Ind.* 953 (1956); M. Yanagita and H. Ogura, *J. Org. Chem.* **23**, 1268 (1958); cf. W. Cocker and T. B. H. McMurry, *Chem. & Ind.* 1430 (1956).
[58] K. Tanabe, *Pharm. Bull. Japan* **6**, 214 (1958).

that alantolactone and isoalantolactone hydrogenate on the α-face of the molecule.

The configuration of the asymmetric centre at C_{11} introduced by hydrogenation of alantolactone (X) or isoalantolactone (LVII) can be deduced[53] from the work of Asselineau *et al.*[59] These workers converted tetrahydroalantolactone (XXXVI) to an isomeric lactone (CIV) by fusion with potassium hydroxide. The conversion can be reversed by a brief treatment with sodium methoxide in methanol, whilst prolonged treatment of tetrahydroalantolactone (XXXVI) with sodium methoxide affords the isomeric lactone (CIV).



XXXVI CIV

These reactions in which the stereochemistry at C_{11} must be involved, are reminiscent of the chemistry of the *cis* fused lactone rings in the desmotroposantonins (see p. 196). The brief sodium methoxide treatment does not open the lactone ring, but C_{11} is epimerised and the lactone with the more stable configuration at C_{11}, i.e. XXXVI is obtained. Fusion with potassium hydroxide or prolonged treatment with methoxide however affords the more stable (at C_{11}) hydroxy-acid or ester, and these will have configuration at C_{11} corresponding to lactone (CIV), which will consequently be formed on acidification.

Sesquibenihiol (XI). The experiments which related[27,30] sesquibenihiol (XI) to tetrahydroalantolactone (XXXVI, p. 188) make it clear that tetrahydrosesquibenihiol must be XLVI.

XI XLVI

α-, and β-Cyperones (VI, VII). Hydrogenation of α-cyperone (VI) using a palladium-charcoal catalyst in ethanol affords a mixture of the *cis* fused tetrahydro derivative CV and the *trans* isomer CVI in the ratio of 11 to 14.[60] Reduction in

VI CV CVI VII

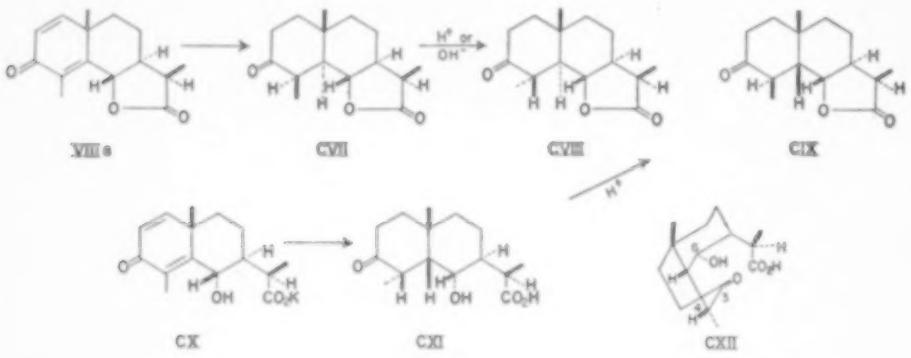
alkaline ethanol gives the *cis* fused tetrahydro derivative, a reaction which involves the enolate.

Reduction of β-cyperone (VII) gives at least some of the *cis* isomer (CV). This must be formed by initial hydrogenation on the α-face of the β-cyperone molecule at the 6:7-double bond followed by desorption from the catalyst and hydrogenation

[59] C. Asselineau, S. Bory, and E. Lederer, *Bull. Soc. Chim. Fr.* 1524 (1955).
[60] R. Howe and F. J. McQuillin, *J. Chem. Soc.* 2670 (1956); 1194 (1958).

of the resulting dihydro compound at the 4:5-double bond from the β-face of the molecule.

Santonin (VIIIa) *and* 11β(H)-*Santonin* (VIIIb). The catalytic reduction of santonin has been studied in several schools.[61] All workers are now agreed that the principal products of catalytic reduction of santonin are the two *trans* fused tetrahydrosantonins CVII and CVIII together with a little of the *cis* isomer CIX.[62,63]



Hydrogenation of potassium santoninate (CX) is comparable with the hydrogenation in alkaline ethanol of α-cyperone (VI), and the *cis* fused hydroxy-acid (CXI) is the main product.[64] Ring closure of the hydroxy-acid takes place with epimerisation at C_4 to give CIX. The stability of the hydroxy-acid at C_4 can be explained if ring A exists in the boat conformation CXII, which would be stabilised by hydrogen bonding between the 6α-hydroxyl and the 3-keto group.[62,63] In CXII, the 4α-methyl group is in the more stable equatorial conformation.

Reduction of 11β(H)-santonin (VIIIb) closely parallels the reduction of santonin itself, and the configuration of the 11-methyl group has little influence on the nature of the products formed.[63,65] With palladised charcoal as catalyst 11β(H)-santonin (VIIIb) affords a mixture of the two *trans* fused tetrahydro compounds CXIII and CXIV, together with a smaller quantity of the *cis* fused isomer CXV and the dihydro compound CXVI.

As in the santonin series the tetrahydro compound CXIII is readily converted either under acid or basic conditions to CXIV with equatorial methyl at C_4. The configurations of the santonin and 11β(H)-santonin reduction products were related[63] by conversion of CXIV to the corresponding tetrahydrosantonin (CVIII) by treatment with potassium carbonate in tetralin.[52,56] Also the 3-desoxy compound (CXVII) derived from the tetrahydro 11(βH)-santonin (CXIV) has been epimerised[66] at C_{11} with sodium methoxide (though it is unaffected by potassium carbonate) to CXVIII,

[61] M. Yanagita and A. Tahara, *J. Org. Chem.* **20**, 959 (1955); A. Tahara, *Ibid.* **21**, 442 (1956); M. Yanagita and R. Futaki, *Ibid.* **21**, 949 (1956); M. Yanagita and H. Ogura, *Ibid*, **22**, 1092 (1957); W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4549 (1956); B. Riniker, Thesis, E.T.H., Zurich (1955); C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6362 (1956); Ö. Kovács, V. Herout, M. Horák, and F. Šorm, *Chem. Listy* **49**, 1856 (1955); *Coll. Czech. Chem. Comm.* **21**, 225 (1956); cf. ref. 1(a), p. 292.

[62] J. C. Banerji, D. H. R. Barton and R. C. Cookson, *J. Chem. Soc.* 5041 (1957).

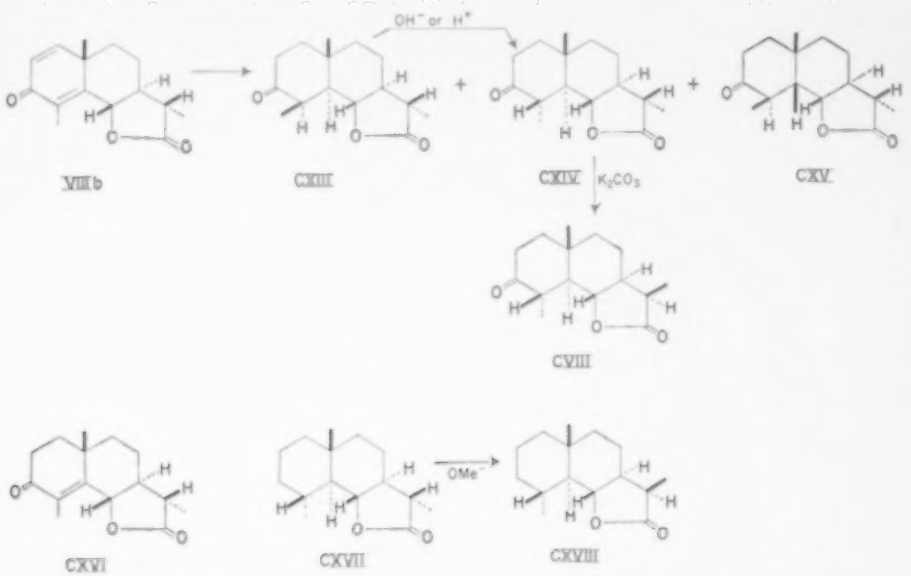
[63] W. Cocker, N. J. H. Dodds, and T. B. H. McMurry, *Tetrahedron* **3**, 160 (1958).

[64] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4549 (1956).

[65] M. Yanagita and H. Ogura, *J. Org. Chem.* **23**, 1268 (1958).

[66] M. Yanagita and H. Ogura, *J. Org. Chem.* **22**, 1092 (1957).

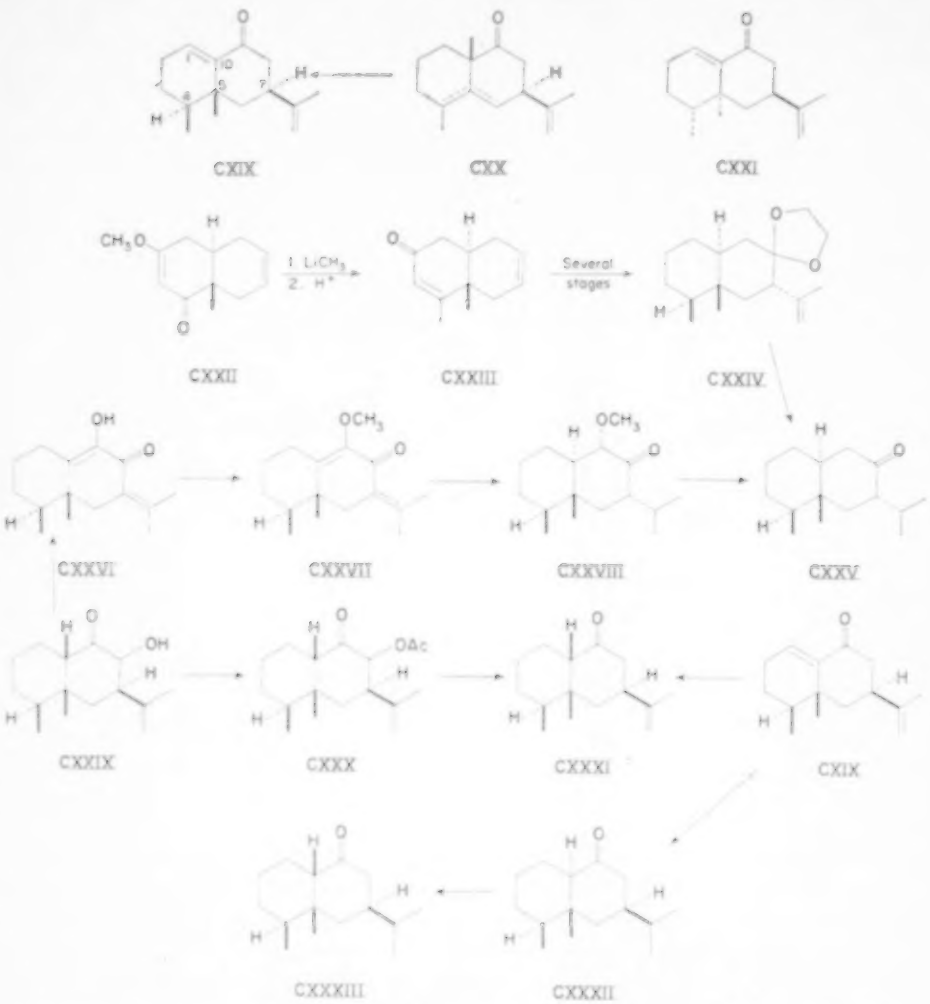
the 3-desoxy compound of the tetrahydrosantonin (CVIII). Such an inversion is expected since as pointed out on p. 198 santonin and its reduced compounds have the more stable configuration at C_{11}.



Eremophilone (CXIX). (Revised, 26 Sept. 1959). Eremophilone is usually looked upon as a member of the eudesmane family, in which the normal isoprene rule is not obeyed. The methyl group is thought[67] to have migrated from C_{10} by a Wagner rearrangement.

The stereochemistry of eremophilone has recently been shown[68,69] to be as in (CXIX), in spite of earlier work[19] which seemed to favour the structure (CXXI). The configuration at C_5 was proved when the dextrorotatory ketone (CXXII), of known absolute configuration[70] was converted to the saturated ketone (CXXV), via (CXXIII) and (CXXIV). The saturated ketone (CXXV) was also obtained from hydroxyeremophilone (CXXVI) by hydrogenation of its methyl ether (CXXVII), equilibration of the resulting ketone with alkali, and demethoxylation of the product (CXXVIII) with calcium in liquid ammonia.[68] Hydroxydihydroeremophilone can be oxidised with bismuth oxide to hydroxyeremophilone (CXXVI) and hence hydroxydihydroeremophilone must have a 5β-methyl group, as in (CXXIX). The orientation of the other asymmetric centres in (CXXIX) follow from an X-ray crystallographic analysis.[71] Hydroxydihydroeremophilone (CXXIX) was converted to its acetate (CXXX) which was reduced with calcium in liquid ammonia to dihydroeremophilone (CXXXI), previously obtained from eremophilone (CXIX) itself. This sequence of reactions cannot involve the centres at C_4, C_5, or C_7 and these must therefore have the same

[67] Sir R. Robinson, cf. A. R. Penfold and Sir J. Simonsen, *J. Chem. Soc.* 87 (1939).
[68] L. H. Zalkow, F. X. Markley and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 2914 (1959).
[69] C. Djerassi, R. Mauli and L. H. Zalkow, *J. Amer. Chem. Soc.* **81**, 3424 (1959).
[70] A. J. Speziale, J. A. Stephens and Q. E. Thompson, *J. Amer. Chem. Soc.* **76**, 5011 (1954).
[71] D. F. Grant and D. Rogers, *Chem. & Ind.* 278 (1956); D. F. Grant, *Acta Cryst.* **10**, 498 (1957).



orientation in eremophilone (CXIX) as in hydroxydihydroeremophilone (CXXIX). Hydrogenation of eremophilone gives the *trans* A/B-fused tetrahydroeremophilone (CXXXII).[19,69] This contains an axial isopropyl group and readily rearranges to give the *cis*-isomer (CXXXIII) where the isopropyl group can be equatorial.

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MOLECULAR STRUCTURE AND ESTROGENIC ACTIVITY—I

UNSYMMETRICAL DIPHENYLETHYLENES AND TRIPHENYLETHYLENES

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VOL. 8 1960

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Abstract—Variation in the planarity of estrogenic substituted ethylenes has been studied by means of U.V. absorption.

1. In the *unsym*-dianisylethylenes, β-substituents increase the steric hindrance. Symmetrical and unsymmetrical twisting of the rings is discussed.

2. Preceding results are extended to trianisylethylene in which different structures are considered: partially non-planar anethole, *cis*-, and *trans*-di-*p*-methoxystilbene. Introduction of a β-chloro atom causes the twisting of all aromatic groups out of the double bond plane. Thus π–π conjugation is considerably reduced giving rise to a new band which is practically not affected by the presence of *para*-methoxy substituents. Increase of estrogenic activity is correlated with this structural modification.

3. Non-planarity alone of a single ring is not sufficient to induce high estrogenic activity, the second ring in the α-position is itself necessary for high activity and the *unsym*-diphenylethylene structure seems to play an important role in the activity of the halogenated-triphenylethylenes. This may explain several findings reported in the literature.

4. The relation between estrogenic activity and structure in these substituted ethylenic compounds should be discussed not only in terms of spatial structure but also as in terms of electron distribution.

THE first workers to indicate any relation between non-planar structure and estrogenic activity were Lewis and Calvin.[1] Jones[2] classified *unsym*-diphenylethylenes, stilbene, substituted stilbenes, and triphenylethylene into two groups, governed by the similarity of the U.V. absorption spectra to those of *trans*-stilbene and styrene. This study is the basis of several subsequent works, and may be summarized as follows.

In the first group (Fig. 1) the maximum at 295 mμ is thought to represent the absorption of a conjugated system along the whole length of the molecule, in which all the carbon atoms are situated along the plane determined by the central double

I II

bond; the resonance energy is maximum. To such a system belong both *trans*-stilbene (I)* and triphenylethylene, which show very similar absorption in the 295

* Molecular dimensions and bond distances are approximate and are drawn only in order to visualize steric effects.

[1] G. N. Lewis and M. Calvin, *Chem. Rev.* **25**, 302 (1939).
[2] R. N. Jones, *J. Amer. Chem. Soc.* **65**, 1818 (1943).

mμ region. In the second group, *unsym*-diphenylethylene (II) and α-β-substituted-ethylenes shows a maximum in the 240 mμ region as does styrene (Fig. 1);

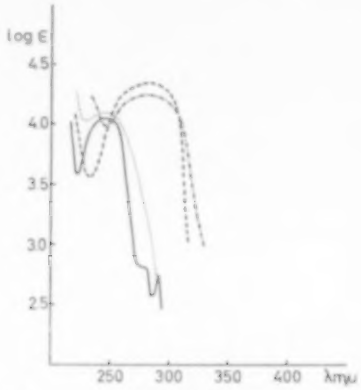

FIG. 1.—styrene (ethanol); . . . . α-β-dimethyl-*trans*-stilbene (ethanol); – – – *trans*-stilbene (chloroform); –.–.–. triphenylethylene (chloroform). (After Jones[2])

Jones has given an empirical interpretation of this result by assuming that the hydrogen atoms situated in the *ortho* position on the adjacent rings (II) are too close to each other, and the hindered structure so obtained is thought to force one of the rings out of the plane of the double bond. In such a case this ring is prevented from being conjugated with the rest of the molecule, and this could explain the fact that the spectrum of the molecule in the region studied is the same as if the ring had been replaced by a hydrogen atom.

Several subsequent studies of the relation between U.V. absorption and estrogenic activity have shown that for stilbene derivatives the presence of such a non-planar structure is significant for estrogenic activity. Jeffrey *et al.*[3] used physical techniques to prove the *trans-trans* structure of dienestrol (α-dienestrol) and *trans*-diethylstilbestrol. In a series of papers Öki,[4] studied diethylstilbestrol and analogues. Recently Grundy[5] has made a general review of this problem, since then Öki[6] has published several interesting studies on the relation between activity and non-planarity in the biphenyl series.

The present paper reports an investigation along the line of the works just mentioned, and its particular purpose is to examine by means of U.V. absorption spectra, the non-planarity in the substituted *unsym*-dianisylethylenes and trianisylethylenes in relation to their estrogenic activity. The importance of the non-planar *unsym*-dianisylethylene group for strong estrogenic activity is discussed.

In connexion with the general problem to which this paper relates, it is appropiate to emphasize here two points which are important for the following discussion and which previous workers have often neglected to mention explicitly:

The relation, between changes in planarity and variations in position and intensity of the bands here considered, is not exact, due to the fact that changes in U.V.

[3] G. A. Jeffrey, H. O. Koch and S. C. Nyburg, *J. Chem. Soc.* 1118 (1948).
[4] M. Öki, *Bull. Chem. Soc. Japan* **26**, 37, 161, 331 (1953); M. Öki and Y. Urushibara, *Ibid.* **25**, 109 (1952).
[5] J. Grundy, *Chem. Rev.* **57**, 281 (1957).
[6] M. Öki, *Bull. Chem. Soc. Japan* **30**, 859 (1957).

absorption reflect differences in conjugation of the various groups and not directly the spatial structure. We shall introduce here a restriction, namely the assumption that the different substituents which are introduced into the molecule do not influence strongly, by their own electronic behaviour, the total electronic state of the molecule. With this restriction, position and intensity of the "K" band can be correlated to the planarity of the molecule.

para-Methoxy derivatives have been used in this study because hydroxylated compounds were not available in every case. This has the disadvantage of introducing one more metabolic step between the injection of the molecule and the action on the biological receptor, if, as it is believed,[5] the molecule has to be demethylated before acting. In trying to establish differences in "inherent" or "true" estrogenic potency between different members of a series is has to be assumed that the splitting of the methyl ether occurs with identical speed for every term of the series and also the absorption and elimination of the estrogen from the body. Such factors are until now unknown and make difficult any attempt to correlate variation in molecular structure with "inherent" or "true" estrogenic activity.

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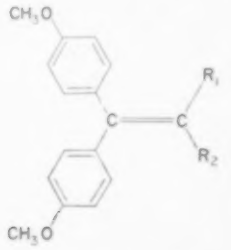
U.V. absorption and estrogenic activity in substituted unsym-*dianisylethylenes*

The U.V. absorption spectra of 1,1-di-*p*-hydroxyphenyl-2,2-diethyl-ethylene ($\alpha\alpha$DE) and its dimethyl ether (III) have been recorded in a preceding report.[7*] They are characterized by a great similarity to the spectra of α-dienestrol and also *trans*-diethylstilbestrol. The position and intensity of the short wavelength band are nearly identical for the three compounds.

Braude,[8] in a study of the 220 mμ band in diphenylmethane, and dibenzyl, has discussed the possibility of interaction of phenyl chromophores through one or two methylene groups. He has also suggested a similar interpretation for the 226 mμ band of the *trans*-stilbene and for the 228 mμ band of the 4,4′-dihydroxy-*trans*-stilbene. All those different bands called E' bands are very similar and are attributed to a partial dibenzyl chromophore.†

The main absorption in di-substituted stilbene is at 240 mμ and may be regarded as a slightly displaced E' band resulting from the partial dibenzyl chromophore,



* It has been found that 1,1-di-*o*-hydroxyphenyl-2,2-diethyl-ethylene described as a new compound has previously been obtained by Z. Földi, and I. Demjén, *Ber. Dtsch. Chem. Ges.* **74**, 930 (1941).

† i.e. a possible interaction of the π electrons of the phenyl rings through the σ electrons of the ethane or ethylene bridge.[8] Similar interactions of a phenyl chromophore with a carbonyl group through a saturated carbon have also been described by W. D. Kumler, L. A. Strait and E. L. Alpen, *J. Amer. Chem. Soc.* **72**, 1463 (1950), who give several other references.

[7] J. F. Miquel, *Acta Chem. Scand.* **12**, 274 (1958).

[8] E. A. Braude, *J. Chem. Soc.* 1902 (1949).

since the band characteristic of the $\pi-\pi$ conjugation has now disappeared because of the non-planarity of the system.

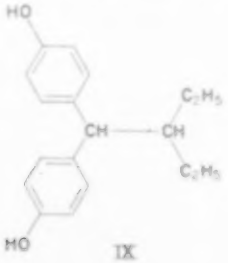
The present result could lend further support to this view, it appears from the findings presented in Table 1 that the 241 mμ band in compound III ($\alpha\alpha$DE dimethyl

TABLE 1

Substituents			First band (E')		Shoulder or second band		Effective dose in mice in micrograms	Mp.	Rf.
No.	R_1	R_2	λ_M	log ε_M	λ_M	log ε_M	50% estrus		
III	C_2H_5	C_2H_5	241	4·29	275–290	3·70	4000	91°	7
IV	H	H	248	4·40	255–270	4·25	Inactive 20 mg	140°	9
V	H	CH_3	245	4·32	255–270	4·25	Inactive 20 mg	99°	9
VI	CH_3	CH_3	241	4·28	...	...	10,000	65°	10
VII	H	C_2H_5	244	4·41	260–270	4·25	Inactive 20 mg	98°	11
VIII	CH_3	C_2H_5	240	4·30	...	...	10,000	49°	12
IX	Ethane deriv		235	4·22	276	3·61	7500	168°	9
Transdiethylstilbestrol			239	4·25	270–280	3·85	0·1	171°	8
Dienestrol			229	4·43	270–280	3·70	0·1	230°	8

ether) and homologues could be assimilated to a *E'* band due to their position and to the fact that, as in the substituted stilbenes, the band is little affected by the presence of hydroxy or alkoxyl substituents. This is not the place to discuss the meanings and the limits of the explanation proposed by Braude for the nature of the 220 mμ and the assimilation of the stilbene's 240 mμ band to such a system but his appealing hypotheses will be accepted in this paper and the short wavelength band of the compound studied called *E'* following his terminology.

Starting from the *unsym*-anisylethylene (IV in Table 1) there is a slight but definite hypsochromic shift of the *E'* band, following the increase in steric hindrance obtained by the introduction of substituents on R_1 and R_2. The reduction in the intensity is parallel. In the case of mono-substitution, the maximum for the methyl derivative is at a shorter wavelength, the intensity is lower, than in the case of the ethyl analogue. The U.V. maxima of *trans*-diethylstilbestrol-dimethylether and α-dienestrol are listed in Table 1 for comparison, and also the ethane derivative of $\alpha\alpha$DE (IX), in which



IX

[9] L. Gatterman, *Ber.* **22**, 1130 (1889).
[10] C. Mentzer and N. Dat-Xuong, *Bull. Soc. Chim. Fr.* 885 (1947).
[11] P. Weill, *Bull. Soc. Chim. Fr.* 1811 (1931).
[12] J. F. Miquel (to be published).

band E' is slightly shifted to shorter wavelengths with a decrease in intensity, and the characteristic shoulder at 270–280 mμ is replaced by a band at 276 mμ. In Table 1 are also listed estrogenic activities of the different compounds. It seems difficult to correlate any variation in steric hindrance with the activity. Campbell[13] who has tested the corresponding ethane derivatives found them active in the range of 5 to 10 mg as free phenol in the Allen–Doisy test with six subcutaneous injections on castrated rats.

Symmetrical twist of the two α rings

In order to explain the similarity in U.V. absorption between styrene and *unsym*-diphenylethylene, and between *trans*-stilbene and triphenylethylene, Jones[2] assumes that in both cases only one ring is twisted out of the double-bond plane. It will be shown below that such a theory meets several difficulties due to certain experimental facts published later and because cpd III seems to prove the necessity for both rings to support a part of the strain. In spite of these objections, Jones' theory has been until now the most valuable basis for investigations concerning the relationship between U.V. absorption, planarity and estrogenic activity.

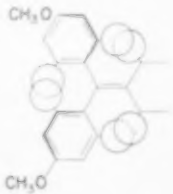
The problem of unsymmetrical twists has been discussed by Ingraham[14] who has compared the estimated energy of a molecule in the case where some rings remain in the plane of the double bond, and in the case where the strain is taken up in as many ways as possible. This last possibility has been found to have more resonance energy and hence predicted to be more stable.

Coates and Sutton[15] have studied the angle formed by the bonds between the phenyl and the α carbon atom in *unsym*-diphenylethylene by electric dipole moment measurements. They found a value greater than the value obtained by calculations but in good accord with bond distance measurements. They concluded both rings must be twisted about 30°.

Interpreting some crystallographic data, Jeffrey *et al.*[3] believe that in *trans–trans*-dienestrol and *trans*-diethylstilbestrol the two rings rotate to the same extent, and remain parallel owing to the existence of centro-symmetry in these molecules.

Braude[8] is against ascribing the E' band to a styrene type of absorption, because in substituted *trans*-stilbene the band at 240 mμ is little affected by substituents, whereas the band at 247 mμ in styrene is displaced to 260 mμ in 4-hydroxystyrene and anethole.

In the cpd III and the ααDE molecule the non-planarity is due not only to the adjacent *ortho* hydrogen atoms of the rings but also to the other *ortho* hydrogen



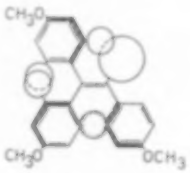
III

[13] N. R. Campbell, *Proc. Roy. Soc.* B **129**, 528 (1940).
[14] L. L. Ingraham, *Steric Effects in Organic Chemistry* p. 490. John Wiley, New York (1956).
[15] G. E. Coates and L. E. Sutton, *J. Chem. Soc.* 567 (1942).

atoms which are hindered by hydrogen atoms from the ethyl group. In such a structure it is not possible for only one of the rings to leave the plane of the double bond; both phenyl rings must contribute to the necessary rotation, and it is reasonable to expect an equal contribution from each of them. Therefore in this β–β di-substituted *unsym*-diphenylethylene it is improbable that a styrene structure plays a part in the E' band. This situation may be different in triphenylethylene where one of the rings may be expected to deviate less from the double-bond plane than the others.

U.V. absorption and estrogenic activity in triphenylethylenes

Among the *para*-hydroxylated triphenylethylenes several interesting estrogenic substances have been reported.[16] Trianisylchlorethylene (X) is used clinically under the name chlorotrianisene (N.N.D.). In the study of triphenylethylene, Jones[2] measurements did not go down to the band at 230 mμ. Following his theory one would have attributed this band to a "styrene-like" structure due to its position. Braude would have agreed since the band changes in position and intensity in the methoxy derivatives.



In trianisylethylene (XI) this band appears at 256 mμ with an intensity: $\log \varepsilon = 4{\cdot}21$. It is intermediate in position and intensity between the planar *trans*-anethole:[17]

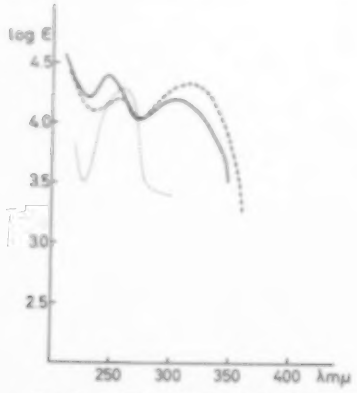


FIG. 2.—trianisylchlorethylene (ethanol); – – – trianisylethylene (ethanol); . . . . anethole (ethanol).

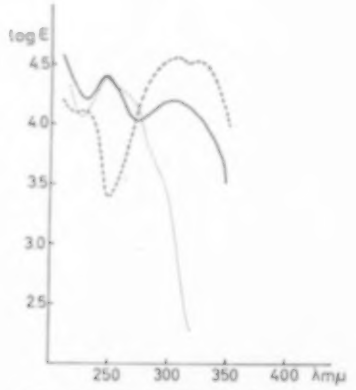


FIG. 3.—trianisylchlorethylene (ethanol); . . . . *unsym*-dianisylethylene (ethanol); – – – di-*p*-methoxy-*trans*-stilbene (ethanol).

259 mμ ($\log \varepsilon = 4{\cdot}34$) and the non-planar *cis*-anethole:[17] 253 mμ ($\log \varepsilon = 4{\cdot}26$) and so can be attributed to a slightly non-planar anethole moiety (Fig. 2). It seems logical to assign this band to the system of the ethylenic double bond in conjugation with the

[16] R. S. Shelton, M. G. Van Campen, D. F. Meisner, E. R. Permerter, E. R. Andrews, R. E. Allen and K. K. Wyckoff, *J. Amer. Chem. Soc.* **75**, 5491 (1953).
[17] Y. R. Naves, P. Ardizio and C. Favre, *Bull. Soc. Chim. Fr.* 566 (1958).

ring in the *cis* position to the hydrogen atom. (Chart I, structure *A*.) Consideration of the Stuart-molecular models also supports this view.

The other band at 315 mμ (log $\varepsilon = 4{\cdot}34$) can be attributed to a "stilbene like" structure (Chart I, structures *B* and *C*.) However, the intensity is smaller than *trans*-di-*p*-methoxy-stilbene (log $\varepsilon = 4{\cdot}56$). The difference might be caused by the lack of planarity of XI. The presence of the *cis*-stilbene structure must be also considered for this band; *cis*-diethyl stilbestrol diacetate[8] shows three bands respectively at 223 mμ (log $\varepsilon = 4{\cdot}16$) 256 mμ (log $\varepsilon = 4{\cdot}00$) and 278 mμ (log $= 3{\cdot}84$). However, as it will be seen below, the contribution of this structure is probably not important.

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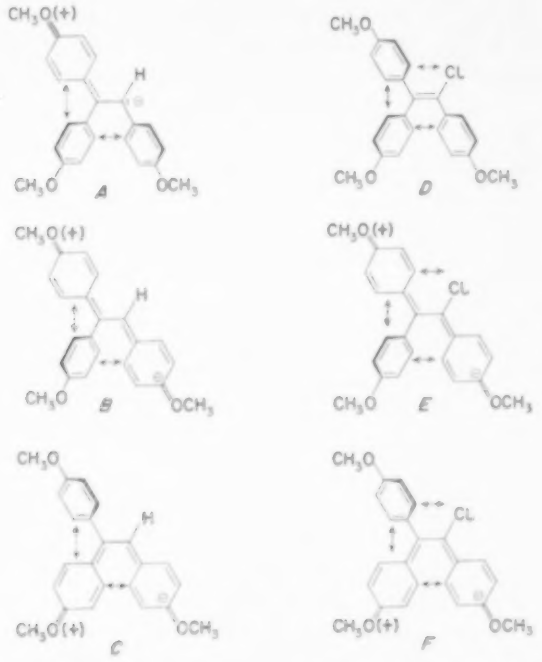


CHART I. Some of the possible resonance structures form 1,1,2-trianisylethylene (*A*, *B*, *C*) and 1,1,2-trianisyl-3-chlorethylene (*D*, *E*, *F*). The symmetrical structures are not drawn. Straight arrow shown represents a strong hindrance; broken arrow represents a less strong hindrance.

The introduction of a chlorine atom at the β-carbon position which increases the estrogenic activity 10 times,[5] provoked a displacement of the anethole-like 256 mμ band to 245 mμ with an increase in intensity to log $\varepsilon = 4{\cdot}40$, which is greater than that of $\alpha\alpha$DE dimethyl ether and *trans*-diethylstilbestrol-dimethyl-ether. The long wavelength band is also shifted to shorter wavelengths but with a decrease in intensity. Thus the band characteristic of conjugation of the same type of structure has disappeared. Hence the structure now seems to be fully non-planar and if the different structures in Chart I: *D*, *E*, *F* are considered, it becomes clear that the new band at 245 mμ must be attributed to an *E'* type band. (Fig. 3.)

The question of the assignment of the long wavelength band remains. As in the

non-chlorinated compounds, the *trans* and *cis* structure must be considered. It is possible to find a partial answer to this problem by considering the fact that the *cis*-stilbene spatial structure (*F*) is not much affected by the introduction of the chlorine atom. Therefore its contribution to the band should remain unchanged and so should the band. Since a hypsochromic shift and a decrease in intensity are observed, the cause is more likely the non-planar *trans*-stilbene structure, which is affected by the chlorine (*E*). Further measurement with *cis* and *trans* substituted triphenylethylenes are necessary to decide the real importance of the contribution of the *cis* structure to the long wavelength band.

As a result of this discussion the short wavelength *E'* band must be attributed to a large extent to the *unsym*-diphenylethylene structure, concurrent with a possible contribution of the non-planar *trans* and *cis* stilbene structure.

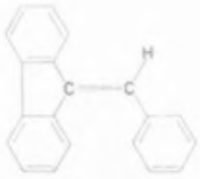
Transformation of the "styrene like" band in trianisyl-ethylene (XI) into a *E'* band in (X) is confirmed by the work of Apelgot *et al.*[18] who have reported the U.V. spectra of triphenylethylene and its β-bromo derivative. Both compounds have their short wavelength maximum at practically the same position (ca. 230 mμ). in spite of differences in planarity. This, however, is due to the lack of methoxyl-groups. In fact the band has a different origin in the two compounds. In the first one it is due to a normal π–π conjugation while in the other it is an *E'* type band.

In the present study the β-substituent of triphenylethylene has been limited to halogen atoms. A verification of these findings should be made by a U.V. investigation of β-alkyltriphenyl-ethylenes[5] and triphenylacrylonitriles.[19] In any case the steric importance attributed to the halogen atom does not mean that its role, as regards the spectrum or the estrogenicity, is limited to this function.

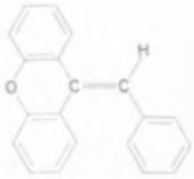
Importance of the two α *rings*

The estrogenic activity in the two series discussed above seems to depend on a non-planar structure, as with *trans*-diethyl-stilbestrol.

The results of Jacques *et al.* who have found compounds (XII and XIII) in which the α rings are incapable of rotation and which are without estrogenic activity at 100 mg doses in rats, tally well with these conclusions.



XII



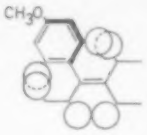
XIII

In order to induce strong estrogenic activity, it is not sufficient that the rings in α and β are both non-planar with respect to the central double bond: *cis*-diethylstilbestrol di-propionate has only 1/600 of the activity of its *trans* isomer,[21] and it has

[18] S. Apelgot, A. Cheutin, S. Mars and M. R. Berger, *Bull. Soc. Chim. Fr.* 533 (1952).
[19] Ng. Ph. Buu-Hoï, L. Corre, A. Lacassagne and S. Lecocq, *Bull. Soc. Chim. Biol.* **23**, 1087 (1947).
[20] J. Jacques, R. Courrier and G. Poumeau-Delille, *Bull. Soc. Chim. Biol.* **27**, 373 (1945).
[21] F. Wessely, A. Bauer, Ch. Chwala, I. Plaichinger and R. Schönbeck, *Monatsh.* **79**, 596 (1948).

been shown that if *cis*-anethole is more active than its planar *trans*-isomer the difference is small.[12]

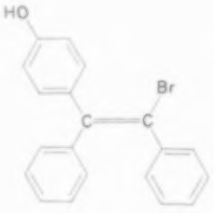
In order to establish whether the second ring is active not merely in inducing non-planar structure but also for more specific reasons compound XIV was prepared. It has the essential features of ααDE (non-planar structure and the same β-substituent). The absorption spectra shows the E_1 band situated at 230 mμ, but the intensity is less than half of that of the ααDE dimethylether, ($\log \varepsilon = 3{\cdot}98$). The shoulder usually found at 270–280 mμ is here transformed into a weaker band at 276 mμ ($\log \varepsilon = 3{\cdot}61$).



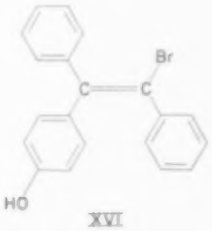
Substance XIV is about 50 times less active in rats than ααDE dimethyl-ether (cpd. III).

These findings also support the importance of the *unsym*-diphenylethylenes structure for estrogenic activity and the fact that this group contributes to the triphenylethylene activity now finds support in the following experimental results previously difficult to explain.

Emmens[22] has prepared the *cis* and *trans* isomers XV and XVI, which produce 50 per cent response in mice, one at 2·7 γ and the other at 3·0 γ. It is well established



XV



XVI

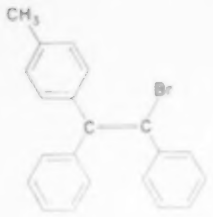
that the presence of an hydroxyl group situated in *para* position on a ring increases considerably the estrogenic activity.* It has also previously been mentioned that a non planar *cis* structure is much less active than a corresponding non planar *trans*-structure. In the case here considered, if the *trans*-stilbene moieties were really determinant for biological activity, the presence of a hydroxyl group on one of the "*trans*" rings in cpd XV would enhance its potency over that of cpd XVI which contains the corresponding *cis*-structure. The lack of a difference in activity between the two compounds indicates the importance of the *unsym*-diphenylethylene part of the molecule.

* J. Jacques (*Bull. Soc. Chim.* 411 (1949)) reports the following figures:

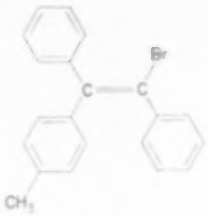
diethylstilbene	inactive 1000 γ
p-hydroxy-diethyl-stilbene	active at 1·2 γ
di-*p*-hydroxy-diethyl-stilbene (stilbestrol)	active at 0·3 γ

[22] C. W. Emmens, *J. Endocriniol.* **3**, 120 (1942).

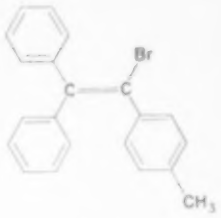
Dvolaitzky and Jacques[23] have recently separated the *cis* and *trans* isomers XVII and XVIII, in which a *para*-methyl group on one of the α rings prevents hydroxylation at that position. In this case too the *cis* and *trans* show nearly the same activity.



XVII



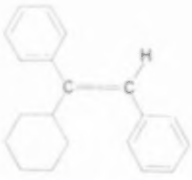
XVIII



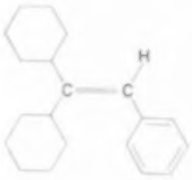
XIX

In spite of the low activity which, as the authors remarked, does not permit any definite conclusions, it is interesting to note that compound XIX, which allows hydroxylation on both α rings, is the most active of the three isomers.

Robson *et al.*[24] have prepared different cyclohexyl analogues of triphenylethylene. Slight activity was found only when two phenyl rings were present in the compound and attached to the same carbon atom.

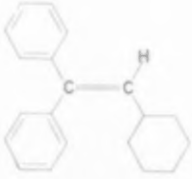


Inactive 20 mg



Inactive 20 mg

The presence of a β-halogen increased the activity of his substance in the same way as the activity of triphenylethylene is increased by the introduction of a halogen.



Active 20 mg

CONCLUSIONS

This study allows us, to include *unsym*-dianisylethylenes and trianisylchlorethylene in a theory based on the "non-planar structure" of the molecule, and in so doing, to make this theory applicable for the most important estrogens in the stilbene series.

[23] M. Dvolaitzky and J. Jacques, *Bull. Soc. Chim. Biol.* **40**, 939 (1958).
[24] J. M. Robson, J. S. H. Davis and W. Tebrich, *Brit. J. Pharmacol.* **5**, 376 (1950).

This study shows also, however, the difficulty in correlating small variations in the planar structure with any appreciable change in estrogenic activity, and a further survey of the literature shows several cases which cannot be explained strictly by a non-planar theory.

In spite of the advances brought by such a theory more refinements have to be introduced in order fully to explain the activity-structure relationships.

In this line an interesting hypothesis has been made by Ōki and Urushibara.[4] They correlate "thickness" and "width" of the molecule, with estrogenic activity. Such a correlation, however, does not seem sufficient to interpret the properties of the compounds under study here, while the thickness of these molecules, probably are almost identical, their width must be quite different, and so also the over-all dimensions of the molecule.

The common factor which seems to be related in a consistent way to the biological properties of our compounds—otherwise rather different from a geometrical point of view—is more probably connected with the presence of the E' band. Therefore the electron distribution has to be considered and so the possibilities of conjugation in addition to spatial factors must also be considered in an attempt to correlate structure with estrogenic activity. Whether or not these estrogenically active substances are fixed on the biological receptor merely because the molecule fits the surface spatially, or whether they adhere due to electronically excited groups on the molecule, or at the end of their conjugated system, is not now known.

Resonance theory has been previously applied to explain the activity of several biologically active substances.[25,26]

Carcinogenic substances belonging to the azo-dyes,[26] stilbeneamine,[27] or amino-biphenyl[28] have been discussed in terms of necessary planar structure and consequently maximum conjugation. Those requirements are in contrast to those which the present author considers important for estrogenic activity.

In the stilbene series for example estrogenic activity requires a non-planar structure which reduces conjugation and preferably two hydroxyl groups; carcinogenic activity has more specific requirements: a fully planar conjugated system and only one amino, or amino substituted, group at the end of the conjugated system. This preliminary comparison between estrogenic and carcinogenic active substances based on variation in conjugation is admittedly speculative but may suggest experimental as well as theoretical research.

EXPERIMENTAL

U.V. Absorption. Recordings were made with Beckman Model DU quartz spectrophotometer, using ethanol solution (concentration 10–20 γ per ml).

Nearly all the substances have been described previously; trianisylethylene and its β-chloro derivative were kindly furnished by Wm. S. Merrell Company N.Y.

1-*p*-Methoxyphenyl-1,2,2-tri-ethyl-ethylene (XIV).

10 g (0·05 mole) *p*-methoxy-2-ethyl-butyrophenone in 30 ml anhydrous ether was slowly added to a Grignard reagent prepared with 6 g ethyl bromide and 2 of magnesium turnings in 50 ml anhydrous

[25] P. Meunier, *La Mésomerie* p. 54. Paris (1947).
[26] A. Pullman and B. Pullman, *Cancérisation par les Substances Chimiques et Structure Moléculaire*. Masson, Paris (1955).
[27] A. Haddow, R. J. C. Harris, G. A. R. Kon and E. M. F. Roe, *Phil. Trans. Roy. Soc.* **241**, 147 (1948).
[28] R. B. Sandin, R. Melby, A. S. Hay, R. N. Jones, E. C. Miller and J. A. Miller, *J. Amer. Chem. Soc.* **74**, 5073 (1952).

ether. After the classical treatment, distillation at 0·5 mm Hg and 95–105° yielded 9 g of a colourless oil (83%). Redistillation at 0·5 mm Hg and 102 gave a colourless, pleasant smelling oil. $n_D^{25} = 1{\cdot}5135$ (Found: C, 82·71: H, 10·27. Calc. for $C_{15}H_{22}O$ (218.33): C, 82·51; H, 10·16%).

Estrogenic activities were determined by the vaginal smear test in ovariectomized mice or rats, the test substances being injected subcutaneously in 0,1 ml olive oil on two succeeding days. The doses shown in Table I, are total doses.

Acknowledgements—I wish to thank Professor E. Bàràny for his interest and his stimulating criticism, and Doctor W. Müller from this Institute for the bio-assays. This work was supported by grants partly from the Swedish Cancer Society, and partly by "Relations Culturelles du Ministère des Affaires Etrangères, Paris".

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SUR L'ACCES AUX 16α-METHYL 17α-HYDROXY STEROIDES

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Résumé—Les 16-méthyl Δ^{16}-pregnènes autorisent une époxydation stéréospécifique en 16–17. Le clivage acide de l'époxyde ainsi obtenu conduit, selon les conditions, soit à un dérivé 16-méthylénique, soit à un 16-méthyl Δ^{15}-pregnène que l'on hydrogène ensuite en 16α-méthyl 17α-hydroxy pregnane correspondant.

L'ouverture réductrice de l'époxyde par le lithium en méthylamine fournit le même arrangement en 16-17.

1. PARTANT d'un dérivé 20-céto 16,17-éthylénique (I), on peut fixer le méthyle en 16α (II) par addition 1-4 du réactif de Grignard et hydroxyler ensuite en 17 (III) par époxydation de l'acétate énolique.[1,2] La méthode se heurte cependant à la stéréospécificité insuffisante de l'époxydation, le méthyl 16α se trouvant en une position symétriquement opposée à celle du méthyle 13β par rapport au carbone trigonal en 17 attaqué par le réactif. Tel n'est pas le cas pour l'éthylénique correspondant (IV) dont le méthyle en 16 est dans le plan même du cycle.[2,3] Nous avons observé que l'époxydation s'opère dès lors exclusivement par l'arrière avec un excellent rendement (V).

Le clivage acide de l'époxyde α ainsi obtenu (V) ne fournit pas les 16β-halogéno 16α-méthyl 17α-hydroxy pregnanes (VI) attendus,[4] mais un mélange de dérivés Δ^{15}-méthylé (VII) et 16-méthylénique (VIII). En particuler, selon nos essais, l'action des hydracides dilués à froid fournit le 16-méthyl Δ^{15}-pregnène (VII), tandis que le chauffage en benzène, en présence d'acide *p*-toluène sulfonique, conduit au méthylénique juxtanucléaire en 16 (VIII). Dans ces conditions d'ailleurs, le composé VII n'est pas stable et fournit le diène (IX), ce qui exclut l'interconversion des deux isomères.

La détermination de la position de la double liaison dans les isomères VII et VIII a été effectuée par deux méthodes indépendantes. D'une part, l'oxydation periodique des glycols 17–20 correspondants (X,XII) a fourni deux cétones isomères (XI, XIII) dont l'une prèsente le spectre caractéristique des 16-méthylène 17-céto stéroïdes. D'autre part, tandis que l'ozonolyse du dérivé méthylénique (VIII) donne 30% de la quantité théorique de formol, le produit principal de la réaction peut être isolé et caractérisé comme un 16-céto stéroïde (XIV).*

L'hydrogénation catalytique des pregnènes isomères VII et VIII produit, à côté du 16β-méthyl pregnane, une quantité variable de dérivé 16α-méthylé (III) selon les

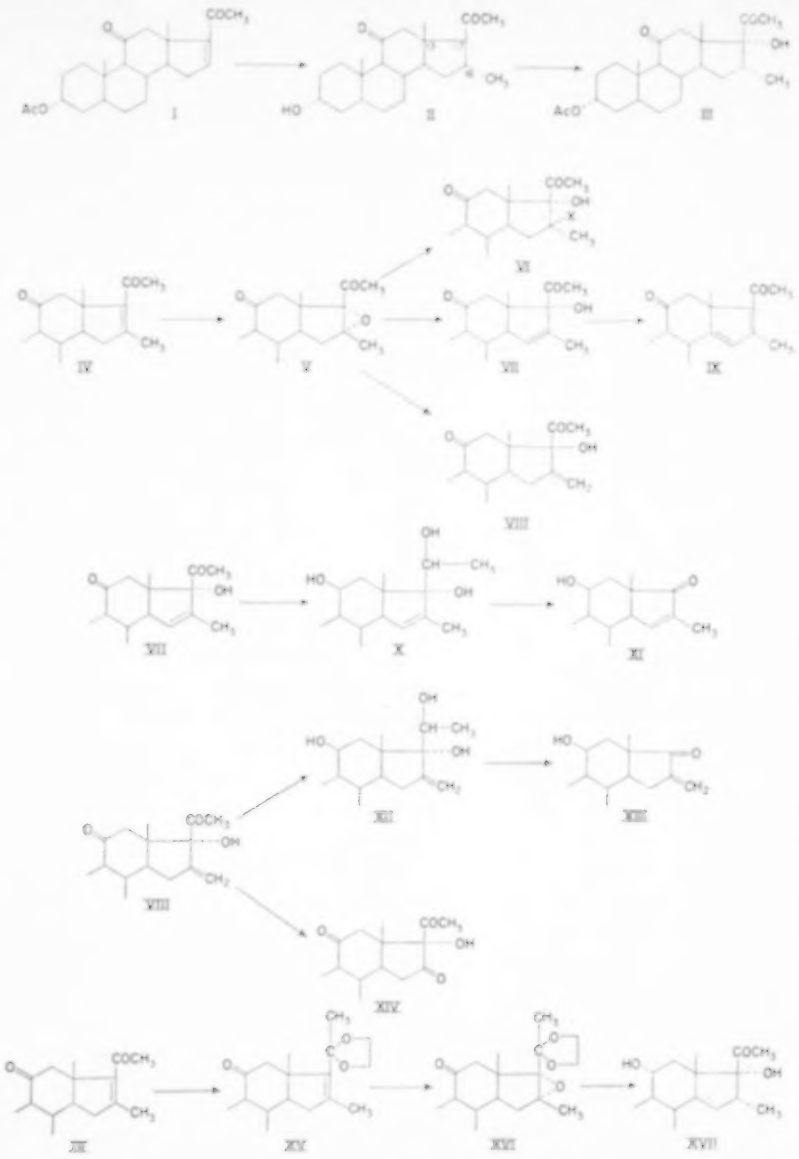
* Communication non publiée du laboratoire de G. Muller (Roussel-Uclaf).

[1] G. E. Arth D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff, L. H. Sarett, *J. Amer. Chem. Soc.* **80**, 3160 (1958).

[2] E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, M. M. Pechet, *J. Amer. Chem. Soc.* **80**, 4428 (1958).

[3] D. Taub, R. D. Hoffsommer, H. L. Slates, N. L. Wendler, *J. Amer. Chem. Soc.* **80**, 4435 (1958).

[4] cf. F. B. Colton, W. R. Nes, D. A. van Dorp, H. L. Mason, E. C. Kendall, *J. Biol. Chem.* **194**, 244 (1952).



conditions choisies. C'est ainsi que l'hydrogénation rapide du Δ^{15}-pregnène (VII), catalysée par le charbon palladié, autorise l'accès au 3α-acétoxy 11,20-dicéto 16α-méthyl 17α-hydroxy pregnane (III) avec un excellent rendement. Ce résultat inattendu semble montrer que la face α des 17α-hydroxy stéroïdes peut présenter un fort encombrement déterminant la stéréospécificité de l'hydrogénation catalytique.

La structure des 16α- et 16β-méthyl pregnanes a été vérifiée par comparaison avec deux échantillons de référence, préparés respectivement selon Arth et Sarett,[1] Oliveto[2] et Taub[3].

2. Nous avons étudié la scission réductrice de l'époxyde 16α-17α (V), qui doit fournir d'emblée le stéroïde 16α-méthyl 17α-hydroxylé.

N'ayant pu préalablement bloquer la fonction 20-cétonique sous forme de cétal en raison de la forte sensibilité de l'époxyde à l'action des acides, nous avons dû inverser les opérations à partir de l'éthylénique Δ^{16}(IV) pour former d'abord le cétal éthylénique (XV), puis l'époxyde (XVI). La décétalisation régénère bien alors l'époxy cétone (V).

L'ouverture réductrice de l'époxyde (XVI) par l'hydrure de lithium et d'aluminium n'a pas été possible, bien que la littérature fournisse quelques exemples de réduction d'oxyranes tétrasubstitués.[5] Nous avons eu recours à la réduction par le lithium en éthylamine.[6] L'attaque s'opère ainsi en 16β. Elle conduit au dérivé 16α-méthyl 17α-hydroxylé (XVII), comme on pouvait le prévoir d'une réduction *trans*. Le carbonyle en 11 fournit l'hydroxyle 11α.

A côté du produit principal, on a isolé, après hydrolyse du cétal, une proportion importante de dérivé 16–17 éthylénique résultant sans doute de la déshydratation du cétal formé par attaque réductrice en 17β. Il suffit de remplacer l'éthylamine par la méthylamine pour favoriser l'attaque en 16 et ne plus obtenir, dès lors, que très peu de dérivé insaturé à côté des 80% du composé 17α-hydroxylé attendu.

Le 3α, 11α, 17α-trihydroxy 16α-méthyl 20-céto pregnane (XVII) se révèle identique au produit de monoréduction en 11 par le sodium dans le propanol du 3α-acétoxy 11, 20-dicéto 16α-méthyl 17α-hydroxy pregnane (III), dont on a protégé le carbonyle en 20 sous forme de cétal.

La même suite de transformations a été effectuée en série 3-cétonique. On accède ainsi au 3,20-dicéto 11α, 17α-dihydroxy 16α-méthyl pregnane, identique au produit d'oxydation sélective en 3 du triol XVII.

PARTIE EXPERIMENTALE

3α-Acétoxy 11, 20-dicéto 16β-méthyl 16α, 17α-époxy pregnane (V). On dissout 1, 5 g de 3α-acétoxy 11, 20-dicéto 16-méthyl Δ^{16}-pregnène (IV)[2] dans 80 cm³ de méthanol, ajoute 3 cm³ de soude 4 N, puis, à 15°, 6 cm³ de perhydrol à 110 vol. Après une nuit à 5°, on verse dans l'eau, lave et recueille 1,2 g d'époxyde libre en 3, F. 177°, $[\alpha]_D = +97°$ ($c = 1\%$, chloroforme). On acétyle au reflux du mélange pyridine-anhydride acétique, recristallise en éthanol et obtient 1, 25 g (80%) du composé V, F. 166°, $[\alpha]_D = +109°$ ($c = 1\%$, chloroforme).
(*Analyse:* $C_{24}H_{34}O_6 = 402{,}5$; Calculé: C, 71,6; H, 8,5; Trouvé: C, 71,8; H, 8,6%)

3α-Acétoxy 11,20-dicéto 16-méthyl 17α-hydroxy Δ^{15}-pregnène (VII). A une suspension de 1 g d'époxyde V dans 3 cm³ d'acétone, on ajoute, à 20°, 1 cm³ d'acide chlorhydrique pur. Après trente minutes à 20°, on verse dans l'eau, essore et lave à l'éther isopropylique. On obtient ainsi 0,9 g (90%) d'éthylénique VII, F.225°, $[\alpha]_D = -8°$ ($c = 1\%$, chloroforme).
(*Analyse*: $C_{24}H_{34}O_6 = 402{,}5$; Calculé: C, 71,6; H, 8,5; O, 19,9; Trouvé: C, 71,8; H, 8,5; O, 20,3%).

La déshydratation de ce composé (0,2 g) est effectuée dans 8 cm³ de benzène auxquels on ajoute 6 mg d'acide *p*-toluène sulfonique. Après distillation de 4 cm³ de benzène, on chauffe pendant une heure au reflux, lave à l'eau bicarbonatée et évapore le benzène. Le résidu, repris en éther isopropylique, fournit 0,13 g (68%) de diène IX, F.184°. Le produit est recristallisé en éthanol pour l'analyse. On obtient 85 mg, F.187°, $[\alpha]_\omega = +345°$ ($c = 1\%$, chloroforme); $\lambda_{max} = 303$ mμ en éthanol ($E^{1\%}_{1cm} = 260$), $\lambda_{infl} = 240$ mμ ($E^{1\%}_{1cm} = 54$).
(*Analyse*: $C_{24}H_{32}O_4 = 384{,}5$; Calculé: C, 75,0; H, 8,4; O, 16,6; Trouvé: C, 74,7; H, 8,4; O, 16,5%). Indice de saponification: Calculé 146; Trouvé 149.

3α-Acétoxy 11,20-dicéto 16-méthylène 17α-hydroxy pregnane (VIII). On dissout 1 g d'époxyde V dans 40 cm³ de benzène et ajoute 35 mg d'acide *p*-toluène sulfonique. On distille 20 cm³ de benzène

[5] L. W. Trevoy, W. G. Brown, *J. Amer. Chem. Soc.* **71** 1675 (1949).
[6] A. S. Hallsworth, H. B. Henbest, *J. Chem. Soc.* 4604 (1957).

et chauffe pendant quatre heures au reflux. Après lavage et évaporation du benzène, on recristallise dans l'éthanol et obtient 0,84 g (84%) de composé méthylénique VIII, F.202°,$[\alpha]_D = -16°$ ($c = 1\%$, chloroforme).

(*Analyse:* $C_{24}H_{34}O_3 = 402{,}5$; Calculé: C, 71,6; H, 8,5; O, 19,9; Trouvé: C, 71,8; H, 8,6; O, 19,8%).

L'ozonolyse de 200 mg de ce composé libère 4,5 mg de formol (titré selon Schryver), soit 30% de la théorie, et permet d'isoler le 3α-acétoxy 11,16,20-tricéto 17α-hydroxy pregnane (XIV), F.200°, $[\alpha]_D = -58°$ ($c = 0{,}25\%$, chloroforme).

(*Analyse*: $C_{23}H_{32}O_6 = 404{,}5$; Calculé: C, 68,3; H, 8,0; O, 23,7; Trouvé: C, 68,4; H, 8,0; O, 24,9%).

Formation et oxydation periodique des glycols 17–20. On dissout 1 g de composé méthylénique VIII dans 35 cm³ de tétrahydrofuran contenant 50% d'eau et ajoute une solution de 0,85 g d'hydroborure de sodium dans 2 cm³ d'eau. On agite pendant cinq heures à 40°, verse dans l'eau, essore et saponifie en potasse méthanolique à 0°. Le tétrol XII obtenu, cristallisé en acétate d'éthyle, fond à 206°.

(*Analyse*: $C_{22}H_{36}O_4 = 364{,}5$; Calculé: C, 72,5; H, 9,95; Trouvé: C, 72,7; H, 10,1%).

La même réduction effectuée à partir du Δ^{15}-pregnène (VII) fournit le tétrol X, F.222°.

L'oxydation de ces tétrols est effectuée dans 60 volumes de méthanol aqueux par 4 parties d'acide periodique pendant cinq heures à température ambiante. Le produit cétonique est isolé à l'aide du réactif T de Girard. Seule la cétone obtenue à partir du composé XII a fourni le spectre des 16-méthylène 17-céto stéroïdes, $\lambda_{max} = 226{,}5$ mμ en éthanol ($\varepsilon = 4530$).

3α-Acétoxy 11,20-dicéto 16α-méthyl 17α-hydroxy pregnane (III). On réduit 5 g de Δ^{15}-pregnène (VII) en solution dans 250 cm³ d'acide acétique pur par agitation en atmosphère d'hydrogène en présence de 12,5 g de charbon à 40% de palladium. Après traitement usuel, on obtient 4 g (80%) de dérivé 16α-méthylé, F.185°. Après recristallisation en acétate d'éthyle pour l'analyse, F.191–192°, $[\alpha]_D = +50°$ ($c = 1\%$, chloroforme).

(*Analyse*: $C_{24}H_{36}O_5 = 404{,}5$; Calculé: C, 71,25; H, 9,0; O, 19,8; Trouvé: C, 71,4; H, 8,9; O, 19,8%).

3α-Acétoxy 11-céto 16-méthyl 20-éthylène dioxy Δ^{16}-pregnène (XV). On traite 5 g de 3α-acétoxy 11,20-dicéto 16-méthyl Δ^{16}-pregnène (IV),[2] dans 200 cm³ de benzène, par 10 cm³ d'éthylène glycol et 0,35 cm³ d'acide perchlorique à 65%. On chauffe pendant cinq heures sous agitation en distillant l'azéotrope benzène-eau. On réintroduit le benzène au cours de l'opération ainsi que deux fois une quantité de 10 cm³ d'éthylène glycol. Après addition d'eau, la phase benzénique est évaporée et le résidu est cristallisé dans le méthanol, puis dans l'éthanol contenant 0,5% de pyridine. On obtient ainsi 3 g (55%) de produit, F.149°, $[\alpha]_D = +59°$ ($c = 1\%$, chloroforme).

(*Analyse*: $C_{26}H_{38}O_5 = 430{,}6$; Calculé: C, 72,5; H, 8,9; Trouvé: C, 72,6; H, 8,8%).

3α-Acétoxy 11-céto 16β-méthyl 16α,17α-époxy 20-éthylène dioxy pregnane (XVI). On dissout 2 g de l'éthylénique XV dans 15 cm³ de dichloréthane puis, à 20°, ajoute 5 cm³ d'éther contenant 1,4 g d'acide perphtalique. Après agitation pendant une nuit à 20°, on essore, lave, distille et cristallise dans l'éthanol. On recueille 1,7 g (80%) d'époxyde XVI, F.210°, $[\alpha]_D = +72°$ ($c = 1\%$, chloroforme).

(*Analyse*: $C_{26}H_{38}O_6 = 446{,}6$; Calculé: C, 69,9; H, 8,6; O, 21,5; Trouvé: C, 70,2; H, 8,7; O, 21,9%).

3α,11α,17α-Trihydroxy 16α-méthyl 20-céto pregnane (XVII). On introduit, à −20°, 2 g d'époxyde XVI dans 60 cm³ de monométhylamine, puis lentement 0,5 g de lithium. On agite pendant cinq heures à −20°, puis ajoute 1 g de chlorure d'ammonium. On évapore la méthylamine, ajoute de l'eau, neutralise puis extrait à l'éther qu'on évapore.

On décétalise à 80° pendant une heure trente dans 20 cm³ d'acide acétique à 80%. Après reprise par l'eau, on neutralise, extrait à l'éther et recristallise dans l'éther isopropylique. On obtient finalement 1,3 g (80%) de triol XVII, F. 210–211°, $[\alpha]_D = +34°$ ($c = 1\%$, éthanol).

(*Analyse*: $C_{23}H_{36}O_5 = 364{,}5$; Calculé: C, 72,5; H, 9,95; Trouvé: C, 72,4; H, 9,9%).

3,20-Dicéto 11α,17α-dihydroxy 16α-méthyl pregnane. Dans le mélange de 0,5 g de triol XVII dans 10 cm³ d'acétone à 33% d'eau on introduit, à 0°, sous agitation, 0,580 g de N-bromo succinimide. On agite pendant deux heures à 0°, puis ajoute 3 gouttes de bisulfite de sodium concentré. On distille l'acétone sous vide puis ajoute de l'eau, essore et cristallise dans l'acétate d'éthyle. On obtient ainsi 0,37 g (75%) du produit d'oxydation sélective en 3, F.197°, $[\alpha]_D = -12°$ ($c = 1\%$, chloroforme).

(*Analyse*: $C_{22}H_{34}O_4 = 362{,}5$; Calculé: C, 72,9; H, 9,45; Trouvé: C, 73,0, H, 9,5%).

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ORGANIC REACTIONS IN STRONG ALKALIS—I

FISSION OF ETHYLENIC ACIDS (THE VARRENTRAPP REACTION)

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Abstract—On treatment with molten potassium hydroxide, ethylenic acids are converted initially into a mixture of isomers, by reversible migration of the double bond in both directions along the chain, and finally into a saturated acid, with two fewer carbon atoms than the starting material, and acetic acid in high yield. A number of minor side-reactions also occur.

The mechanisms of these processes are discussed.

NUMEROUS studies have been made on the behaviour of organic compounds in strongly alkaline media, but many of the reactions involved are still only poorly understood. Furthermore the extensive literature on the subject contains many conflicting and unexpected reports. A general study of organic reactions in strong alkalis was therefore initiated in 1953, and the results will be given in this series of papers,

Our first objective is to examine the behaviour of the main aliphatic functional groups in concentrated alkali hydroxides. For this purpose the fatty acids and their derivatives afford an ideal series of compounds; they enable the grouping under investigation to be readily introduced into the reaction medium, and give rise to products which are conveniently analysed chromatographically. During previous investigations with these compounds suitable techniques for analysis of the starting materials and products were often not available, and, in consequence, many misleading claims have been made. A preliminary account of our own studies has already been given.[1] In this paper we are concerned mainly with the fission of olefinic acids in molten alkalis.

In 1840 Varrentrapp[2] heated oleic acid (I) with molten potassium hydroxide and obtained palmitic acid, acetic acid and hydrogen. For many years oleic acid was formulated, largely on this evidence, as octadec-2-enoic acid, and the nature of the transformation involved in the Varrentrapp reaction was not fully appreciated until the advent of reliable degradative procedures enabled the correct structure of oleic acid to be deduced.[3] Other similar fatty acids which have been converted by alkali

$$CH_3\cdot(CH_2)_7\cdot\overset{cis}{CH}{:}CH\cdot(CH_2)_7\cdot CO_2H \longrightarrow CH_3\cdot(CH_2)_{14}\cdot CO_2H + CH_3\cdot CO_2H + H_2$$

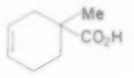
II

[1] *Chem. & Ind.* 402 (1958).
[2] F. Varrentrapp, *Liebigs Ann.* **35**, 196 (1840).
[3] cf. T. P. Hilditch, *The Chemical Constitution of Natural Fats.* Chapman and Hall, London (1947) F. D. Gunstone, *Chem. & Ind.* 250 (1955).

fusion* into saturated acids containing two fewer carbon atoms include elaidic,[2] erucic,[4] brassidic,[5] and undecylenic acid,[6] and thus the reaction is clearly general for both *cis* and *trans* ethylenic fatty acids. An interesting variant is the formation of pimelic acid from cyclohex-3-ene-carboxylic acid (II),[7,8] the loss of two carbon atoms being avoided with this cyclic starting material.

Although almost quantitative yields were claimed by some early investigators,[9,10] these were not achieved by many subsequent workers who often failed to appreciate the importance of carrying out the reaction in an inert atmosphere. We find that when this precaution is taken yields of about 80 per cent are readily obtained, but that yields drop to 50 per cent or less when no attempt is made to exclude air.

The mechanism of the Varrentrapp reaction has been the subject of much speculation. Although Chuit *et al.*[11] interpreted their results with undecylenic acid as indicating fission of the double bond at positions remote from the carboxyl group, most authors have argued that the double bond, or some group derived from it, first migrates into the $\alpha\beta$ position and then undergoes fission.[8,10,12] Strong support for this view is provided by the observation that neither 1-methylcyclohex-3-ene-1-carboxylic acid (III),[7] nor 3:3-dimethylnon-8-en-1-oic acid (IV),[13] in which the α and β positions respectively are blocked, exhibit the normal Varrentrapp reaction. However $\alpha\beta$-unsaturated acids (e.g. V, $n = 2$,[14] 4,[14] 8[15] and 14;[16] cyclohex-1-enylcarboxylic acid[7,17]) are readily split under similar conditions.



III

$CH_2{:}CH.(CH_2)_4.CMe_2.CH_2.CO_2H$

IV

V $\quad CH_2{\cdot}(CH_2)_n{\cdot}CH{:}CH{\cdot}CO_2H \longrightarrow CH_2{\cdot}(CH_2)_n{\cdot}CO_2H + CH_2{\cdot}CO_2H$

Moreover Hunter and Popják[14] have demonstrated that hex-2-enoic and oct-2-enoic acid give acetic acid and either butyric or hexanoic acid in roughly equivalent amounts. A similar relationship between the two main fission products has now been established for the non-conjugated acid, undec-10-enoic acid.

Hydroxy-, keto- and dihydroxy-acids[6,10,18] have been postulated as intermediates in the migration stage of the Varrentrapp reaction, but their participation is excluded

* In this series "alkali fusion" will refer to a reaction with an alkali metal hydroxide in which the reagent is liquid at the reaction temperature but solid at room temperature.

[4] A. Fitz, *Ber. Dtsch. Chem. Ges.* **4**, 442 (1871).
[5] G. Goldschmidt, *Jahresbericht* 522 (1877).
[6] F. Becker, *Ber. Dtsch. Chem. Ges.* **11**, 1412 (1878); F. Krafft, *Ibid.* **15**, 1687 (1882); I. Jegorow, *J. Russ. Phys. Chem. Soc.* **46**, 975 (1914); *Chem. Zentr.* **I**, 934 (1915); R. Shagalova, *Masloboino Zhirovoe Delo* **11**, 452 (1935); *Chem. Abstr.* **30**, 1026 (1936).
[7] H. J. Pistor and H. Plieninger, *Liebigs Ann.* **562**, 239 (1949).
[8] F. X. Werber, J. E. Jansen and T. L. Gresham, *J. Amer. Chem. Soc.* **74**, 532 (1952).
[9] W. L. Carpenter, *J. Soc. Chem. Ind.* **2**, 98 (1883).
[10] F. G. Edmed, *J. Chem. Soc.* **73**, 627 (1898).
[11] P. Chuit, F. Boelsing, J. Hausser and G. Malet, *Helv. Chim. Acta* **9**, 1074 (1926); **10**, 113 (1927).
[12] M. Saytzeff, C. Saytzeff and A. Saytzeff, *J. Prakt. Chem.* **37**, 269 (1888).
[13] R. Lukeš and J. Hofman, *Chem. Listy* **52**, 1747 (1958).
[14] G. Hunter and G. Popják, *Biochem. J.* **50**, 163 (1951).
[15] C. H. Kao and S.-Y. Ma, *J. Chem. Soc.* 2046 (1931).
[16] G. Ponzio, *Gazzetta* **34**, 77 (1904).
[17] F. Runge, R. Hueter and H.-D. Wulf, *Chem. Ber.* **87**, 1430 (1954).
[18] G. Wagner, *Ber. Dtsch. Chem. Ges.* **21**, 3347 (1888).

by alkali fusions of authentic compounds of these types.[1,19,20] A prototropic mechanism was first advanced by Farmer[21] in 1942, and receives support from the work of Lüttringhaus[22,23] and Pines[24] on the metallation of simple olefins. With the reservation that proton removal and proton return may be either consecutive or concerted processes, the mechanism may be represented in the following way.

By a sequence of such transformations the double bond might be expected to migrate into all available positions, though no true equilibria would be established owing to the removal by fission of the $\alpha\beta$-isomer. However Farmer reported that on treatment of oleic acid with molten alkali the double bond migrated solely towards the acid function, and attributed this rather surprising result to the inductive effect of the carboxylate group. Considering that a chain of seven carbon atoms originally separates the two functional groups, such an explanation cannot now be accepted. We have therefore studied the migration of double bonds under the conditions of the Varrentrapp reaction.

Oleic acid was heated with potassium hydroxide at 300° (bath temp) for various times insufficient to cause complete reaction, and the products examined (Table 1). The loss of unsaturated acid was calculated from the iodine value of the product, and the amount of palmitic acid formed was determined by gas–liquid chromatography after esterification with methanol. The good agreement between the two values showed that saturated intermediates did not accumulate during the reaction, and that the products consisted mainly of palmitic acid and mixtures of octadecenoic acids.

Information on the nature of the residual octadecenoic acids was obtained by careful ozonolysis of the fusion products, and analysis of the resulting dicarboxylic acids by paper chromatography; an octadec-n-enoic acid thus yielded a C_n-diacid. To minimize side reactions (see p. 236) the oxidations were not carried to completion, but the relative amounts of the diacids reflected the proportions of the original octadecenoic acids. The monocarboxylic acids obtained on ozonolysis of the 30 and 120 min fusion products were examined by gas-liquid chromatography of their methyl esters, and shown to contain the C_7 to C_{10} acids in roughly the same relative proportions as the complementary dicarboxylic acids. These results demonstrated the formation of all isomeric octadecenoic acids from Δ^4 to Δ^{12} (others were doubtless formed but were not detected by the analytical procedure used, see p. 236). It is clear that, contrary to Farmer's claim, *the double bond migrates initially almost equally in both directions*, and that the carboxylate group exercises no directing influence during the early stages of the reaction. Since these findings, the formation of small amounts of both octadec-8- and octadec-10-enoic acids on alkali fusion of oleic acid at 280°–300° has been reported by Blekkingh *et al.*[25]

Infra-red spectrophotometry of the fusion products showed that the proportion of the residual octadecenoic acids with the *trans* configuration rose with the time of

[19] A. Eckert, *Monat.* **38,** 1 (1917).
[20] R. A. Dytham and B. C. L. Weedon, *Tetrahedron* **8,** 246 (1960);
[21] E. H. Farmer, *Trans. Faraday Soc.* **38,** 356 (1942).
[22] A. Lüttringhaus, G. Wagner-v. Sääf, E. Sucker and G. Borth, *Liebigs Ann.* **557,** 52 (1947).
[23] cf. H. Gilman and R. L. Bebb, *J. Amer. Chem. Soc.* **61,** 109 (1939).
[24] H. Pines, J. Vesely and V. N. Ipatieff, *J. Amer. Chem. Soc.* **77,** 347 (1955).
[25] J. J. A. Blekkingh, H. J. J. Janssen and J. G. Keppler, *Rec. Trav. Chim.* **76,** 35 (1957).

reaction from 0 to ca. 65 per cent. The latter value agrees well with that found in the equilibrium between oleic and elaidic acids.[3] One fusion product was separated by the lead salt procedure[26] into solid and liquid fractions, the former composed mainly of the saturated and *trans*-acids, and the latter mainly of the *cis*-acids. The solid and liquid fractions contained 60 and 40 per cent respectively of the total unsaturation, and both were shown by oxidation to contain all octadecenoic acids from Δ^6 to Δ^{11}

Table 1. Alkali fusion of oleic acid at 300° (bath temp)

		30 min	60 min	90 min	120 min
I.V. of product		87·8	79·8	71·5	61·4
octadecenoic acids lost (mol %)[a]		3	12	22	34
palmitic acid formed (mol %)		~3	15	27	35
trans-octadecenoic acids (mol %)[b]		46	59	63	67
Yield (mol % of diacids from ozonolysis of fusion product)[c]	C_{12}	—	—	—	(0.4)
	C_{11}	(0·8)	(0·9)	(0·9)	(1·6)
	C_{10}	13·1	9·9	8·3	4·3
	C_9	42·6	15·0	6·1	7·9
	C_8	11·7	7·9	6·5	8·1
	C_7	2·3	2·2	3·7	3·1
	C_6	1·4	1·4	3·9	2·1
	C_5	[0·3]	1·1	2·4	1·2
	C_4	[0·7]	1·5	3·4	2·7
	Total	72·9	39·9	35·2	31·4

[a] Calculated from I.V. of product without allowance for the formation of unsaturated polymers.
[b] Based on residual octadecenoic acids.
[c] Figures in parentheses ( ) probably indicate too low, and those in brackets [ ], too high, a value for the corresponding ethylenic acid (see p. 237)

in about the same proportions. As the lead salt technique gives somewhat low values for *trans*-acids in multicomponent mixtures,[27] it may be concluded that each octadecenoic acid formed by double bond migration is an equilibrium mixture of *cis* and *trans* forms. The presence of octadec-*trans*-9-enoic acid indicates reformation of the Δ^9-acid, by further rearrangement of the other isomers. All these findings are consistent with the prototropic mechanism envisaged for the isomerization stage of the Varrentrapp reaction.

In another series of experiments oleic acid was heated with molten potassium hydroxide at temperatures ranging from 260° to 380°. The results (Table 2) were generally similar to those already described. At 260° very little fission occurred, even after reaction for 5 hr.

In both the time and temperature studies, the yield of dicarboxylic acids obtained

[26] L. V. Cocks, B. C. Christian and G. Harding, *Analyst* **56**, 368 (1931).
[27] F. L. Jackson and J. E. Callen, *J. Amer. Oil Chem. Soc.* **28**, 61 (1951).

on oxidation dropped markedly with diminution in the iodine value of the fusion product. Spectroscopic examination of these products showed no significant amounts of the $\alpha\beta$-unsaturated acid (the formation of octadec-2-enoic acid on heating oleic acid with aqueous alkali in oxygen has been reported,[28] though the evidence is not conclusive). The absence of any substantial amount of the $\beta\gamma$-isomer was established by ozonolysis, and gas–liquid chromatography of the methyl esters of the resulting

TABLE 2. ALKALI FUSION OF OLEIC ACID AT VARIOUS TEMPERATURES
(30 min unless stated otherwise)

		260°	280°	300°	260°*	320°	360°	380°	360°†
I.V. of product		87·8	87·8	87·8	87·0	62·3	21·0	10·2	5·8
octadecenoic acids lost (mol %)[a]				3		33	78	88	94
palmitic acid formed (mol %)				~3		~40			
trans-octadecenoic acids (mol %)[b]		2	17	46		56			
Yield (mol %) of diacids from ozonolysis of fusion product[b,c]	C_{12}	—	—	—	—	(0·7)	(0·4)	(0·06)	5·5
	C_{11}	—	—	(0·8)	(0·5)	(1·8)	(8·7)	(1·3)	5·5
	C_{10}	—	6·8	13·1	6·4	18·7	7·7	3·1	3·8
	C_9	55·3	41·9	42·6	42·3	24·7	6·7	2·3	1·9
	C_8	1·9	6·2	11·7	9·9	15·0	4·7	0·43	—
	C_7	1·8	1·0	2·3	3·0	2·8	1·4	0·08	—
	C_6	[0·5]	[0·5]	1·4	[0·4]	1·4	0·6	0·06	—
	C_5	[0·8]	[0·3]	[0·3]	[0·5]	1·0	0·3	0·04	—
	C_4	[1·3]	[0·5]	[0·7]	[0·8]	1·0	—	0·09	—
	Total	61·6	57·2	72·9	65·0	67·1	30·5	7·5	16·7

[a,b,c] See footnotes to Table 1.
* Reaction time 300 min
† Reaction time 60 min

acids, which revealed only traces of methyl pentadecanoate. Since ozonolysis of authentic mixtures of palmitic acid with small amounts of oleic acid gave satisfactory results, the low yields referred to above indicate that compounds other than the Δ^2 to Δ^{12} octadecenoic acids account for much of the residual unsaturation in products of low iodine value. These compounds may include octadecenoic acids with double bonds in positions remote from the carboxyl group, and unsaturated polymers formed by intermolecular addition reactions (see below).

Another feature of the above results is that, although the distribution of the double bond along the chain became more uniform as the reaction proceeded, no large amount of the Δ^2 to Δ^7 octadecenoic acids was ever detected. (Jegorow's[6] claim to have isolated octadec-5-enoic acid after heating oleic acid with concentrated aqueous alkali could not be confirmed.) It therefore seemed desirable to study the fusion of ethylenic acids with the double bond originally in such positions.

[28] W. Treibs and M. Rothe, *Chem. Ber.* **84**, 370 (1951).

The results (Table 3) from the alkali fusion of petroselinic acid (VI) under a variety of conditions resembled those obtained with oleic acid. The monocarboxylic acids obtained on ozonolysis of the fusion products were those to be expected from analyses of the complementary dicarboxylic acids, and the relative proportions were similar. Double bond migration occurred in both directions; in one experiment (300°/1 hr) nearly all the residual unsaturation detected was in positions further from the

TABLE 3. ALKALI FUSION OF PETROSELINIC ACID

	250°/30 min	280°/30 min	300°/30 min	300°/60 min	360°/30 min
I.V. of product	86·2	56·5	32·0	18·2	2
octadecenoic acids lost (mol %)[a]	3	39	66	81	98
palmitic acid formed (mol %)	~1		58	84	
trans-octadecenoic acids (mol %)[b]	10	24	69		
Yield (mol %) of diacids from ozonolysis of fusion product[a]: C_{11}	—	—	—	—	
C_{10}	—	—	—	0·9	
C_9	—	—	0·3	1·5	
C_8	—	—	4·2	8·9	
C_7	2·3	4·0	8·6	19·5	
C_6	67·3	45·3	27·8	2·0	
C_5	3·0	11·1	3·4	—	
C_4	3·6	4·5	1·6	—	
Total	76·2	64·9	45·9	32·8	

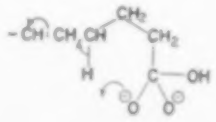
[a,b] See footnotes to Table 1.

carboxylate group than the original Δ^6 position. However, even before any appreciable fission had occurred, there was more migration towards, than away from, the acid function.

$CH_3{\cdot}(CH_2)_{10}{\cdot}\overset{cis}{CH{:}CH}{\cdot}(CH_2)_4{\cdot}CO_2H$ VI

$CH_3{\cdot}(CH_2)_{14}{\cdot}\overset{trans}{CH{:}CH}{\cdot}CO_2H$ VII

A direct comparison (Table 4) of the behaviour of oleic, petroselinic and $\alpha\beta$-oleic (VII) acids under the same conditions showed that the rate of reaction increased with the proximity of the original double bond to the carboxyl group. It is conceivable that double bonds in the Δ^4 and Δ^5 positions, and perhaps, to a lesser extent, even



VIII

those at Δ^6 and Δ^7, react faster than those in the Δ^9 and more remote positions due to the operation of an intramolecular mechanism. This may be represented for the Δ^5-isomer by VIII.

Similar proposals have been made by Jones *et al.*[29] to account for the more rapid isomerization in concentrated alkalis of pent-4-ynoic and hex-5-ynoic acid compared with higher ω-acetylenic acids. It has previously been reported that Δ^4-ethylenic acids are hardly affected by treatment with alkali, in marked contrast to the Δ^2 and

TABLE 4. ALKALI FUSION OF OCTADECENOIC ACIDS
(300° bath temp/30 min)

		$\Delta^{9:10}$	$\Delta^{6:7}$	$\Delta^{2:3}$
I.V. of product		87·8	32·0	13·1
octadecenoic acid lost (mol %)[a]		3	66	87
trans-octadecenoic acids[b]		46	69	
Yield (mol %) of diacids from ozonolysis of fusion product[b,c]	C_{11}	(0·8)	—	—
	C_{10}	13·1	—	—
	C_9	42·6	0·3	—
	C_8	11·7	4·2	—
	C_7	2·3	8·6	—
	C_6	1·4	27·8	—
	C_5	[0·3]	3·4	—
	C_4	[0·7]	1·6	3·0
	Total	72·9	45·9	

[a,b,c] See footnotes to Table 1.

Δ^3 isomers which undergo rapid equilibration;[30] the conditions (30 per cent KOH/100°) were, however, far less drastic than those used in the present studies.

When octadec-2-enoic acid was heated with potassium hydroxide at 300° for 30 min, fission was incomplete (Table 4). The composition of the residual (13 per cent) octadecenoic acids was estimated as 85 per cent of the Δ^2-isomer (determined by ultra-violet light absorption), 12 per cent of the Δ^3-isomer (determined by ozonolysis and analysis of the resulting acids by gas–liquid chromatography of their methyl esters), and 3 per cent of the Δ^4-isomer (determined by oxidation to succinic acid). The rapid equilibration of $\alpha\beta$- and $\beta\gamma$-ethylenic acids in alkalis is well known,[30,31] but the formation of some Δ^4-isomer from octadec-2-enoic acid is interesting. Crossley and Hilditch[32] reported that, when heated with potassium hydroxide in glycol at 170–180°, deca-2:4-dienoic acid appeared to give mainly the $\Delta^{4,6}$- and

[29] E. R. H. Jones, G. H. Whitham and M. C. Whiting, *J. Chem. Soc.* 3201 (1954).
[30] A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.* 2343 (1928); R. P. Linstead and E. G. Noble, *Ibid.* 614 (1934).
[31] J. Cason and G. Sumrell, *J. Org. Chem.* **16**, 1181 (1951); J. Cason, N. L. Allinger and G. Sumrell, *Ibid.* **18**, 850 (1953).
[32] A. Crossley and T. P. Hilditch, *J. Chem. Soc.* 4613 (1952).

$\Delta^{5,7}$-isomers, and a thermal rearrangement of 5-methyltridec-2-enoic acid to the Δ^4-isomer has been claimed by Cason *et al.*[33]

The interconversion of Δ^2- and Δ^3-isomers in molten alkalis was more conveniently demonstrated with non-2-enoic acid. After brief treatment with potassium hydroxide (ca. 280°/3 min) a mixture containing ca. 70 per cent of the Δ^2-isomer and ca. 20 per cent of the Δ^3-isomer was recovered (cf. 74 per cent $\alpha\beta$- and 26 per cent $\beta\gamma$-isomer

Table 5. Alkali fusion of undec-10-enoic acid

		250°/60 min[a]	300°/30 min	300°/60 min	300°/90 min	360°/60 min
I.V. of product		132	127·7	70·3	43·3	<1
undecenoic acids lost (mol %)[a]		—	8	50	70	99
trans-undecenoic acids (mol %)[d]		68				
Yield (mol %) of diacids from ozonolysis of fusion product[b]	C_{10}	5	4·1	1·9	1·8	
	C_9	48	17·0	14·5	20·3	
	C_8	15	13·3	10·0	15·3	
	C_7	2	7·2	8·6	8·1	
	C_6	—	5·3	6·1	6·0	
	C_5	—	2·8	3·1	2·4	
	C_4	—	4·2	3·8	1·4	
	Total	70·0	53·9	48·0	55·3	

[a] Dicarboxylic acids from ozonolysis of fusion products were analysed by G.L.C. of their methyl esters.
[a,b] See footnotes to Table 1.
[d] Based on undecenoic acids other than Δ^{10}

from equilibration of hex-2-enoic acid in aqueous potassium hydroxide[30]). Under more drastic conditions (300°/5 min), heptanoic acid was produced.

Both Jegorow[6] and Eckert[19] demonstrated that undec-10-enoic acid could be converted by treatment with concentrated alkalis into a product consisting mainly of the Δ^9-isomer. Later Chuit *et al.*[11] stated that alkali fusion of undec-10-enoic acid gave not only nonanoic acid, as reported by Becker,[6] but also small amounts of the next four lower homologues. They concluded that the Δ^9-isomer and, subsequently, small amounts of other isomers were first formed by rearrangement, and that fission of the double bond in the various positions then gave the observed products. An initial rapid migration of the double bond into the penultimate position is to be expected, as di-alkylated ethylenes are thermodynamically more stable than their mono-substituted isomers, but we believe the conclusions of the Swiss authors concerning fission to be incorrect. Examination of the products from various alkali fusions of undec-10-enoic acid (Table 5) indicated that the double bond migrated rapidly away from the terminal position, and then along the chain. (After the completion of this investigation Lüttringhaus and Reif[34] reported the migration of the double bond as

[33] J. Cason, N. L. Allinger and C. F. Allen, *J. Org. Chem.* **18**, 857 (1953).
[34] A. Lüttringhaus and W. Reif, *Liebigs Ann.* **618**, 221 (1958).

far as the Δ^6 position on heating undec-10-enoic acid with methanolic alkalis, an 82 per cent conversion into the Δ^9-isomer being achieved under some conditions. Their conclusions concerning the course of the Varrentrapp reaction are in many respects similar to ours.) The di-substituted double bonds formed by rearrangement were shown (infra-red spectra) to be equilibrium mixtures of the *cis* and *trans* forms. The greater reactivity of undec-10-enoic acid compared with oleic acid (cf. Tables 1 and 5) may be partly due to the absence of any stable double bond position more remote than Δ^9 from the carboxylic group. Complete reaction of undec-10-enoic acid gave nonanoic acid in 80 per cent yield; only traces of lower homologues were observed (cf. Chuit *et al.*[11]), and these probably arose from side reactions of the types discussed later.

All the information presented above is consistent with the view that *alkaline fission of an ethylenic acid occurs by reversible migration of the double bond along the chain until it reaches the $\alpha\beta$-position, where it undergoes irreversible fission.* There is as yet no evidence to suggest that either inter- or intramolecular hydrogen transfer leads to an $\alpha\beta$-ethylenic acid more directly. Both processes are unlikely. Moreover the former would result in equimolecular amounts of two saturated acids, one containing the same number of carbon atoms as the starting material and the other four fewer (cf. Part II); such products are not observed to any significant extent in Varrentrapp reactions.

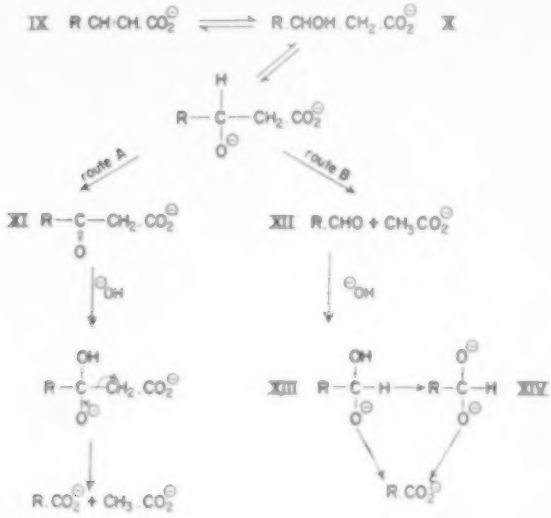
Considering now the fission of the $\alpha\beta$-ethylenic acids (IX), it seems most likely that this involves an initial nucleophilic attack by hydroxyl ions to give a β-hydroxy-acid (X). The formation of β-hydroxy-acids during the alkaline equilibration of $\alpha\beta$- and $\beta\gamma$-ethylenic acids has been reported.[35–37] Such hydrations are reversible; when heated with alkali, crotonic acid gives β-hydroxybutyric acid,[38] and the latter yields crotonic acid together with small amounts of vinylacetic acid.[36] The conversion of 2-hydroxycyclohexane-1-carboxylic acid into cyclohexene-1-carboxylic acid in concentrated alkalis has also been described.[7,8] Although β-hydroxy-acids have not been isolated from alkali fusions of ethylenic acids, this is probably due to their ease of fission. Alkali fusion of β-hydroxystearic and β-hydroxybutyric acid gave palmitic acid and (1·9 moles) acetic acid respectively.

There are two plausible mechanisms for the breakdown of a β-hydroxy-acid. Either dehydrogenation occurs ("route A"), followed by normal "acid fission" of the resulting β-keto-acid (XI), or fission by a reaction of the "retro-aldol" or "retro-Claisen" type gives acetate and an aldehyde (XII), which is then converted into the corresponding acid ("route B"). The dehydrogenation in alkalis of other hydroxy-acids to keto-acids has recently been demonstrated,[20] but alkali fusion of 3-oxobutyric acid, 3-oxodecanoic acid and methyl 3-oxo-octadecanoate gave neutral by-products which were not observed during Varrentrapp reactions (the formation of small amounts of cyclohexanone during the conversion of cyclohexenecarboxylic acids into pimelic acid has been noted,[8] but may have resulted from pyrolysis of the main product, sodium pimelate). Such by-products were produced in the alkali fusion of dec-2-ynoic acid where there is good reason to believe that a β-keto-acid is implicated (Part II). The view that decarboxylation of a β-keto-acid first formed gave a ketone which then

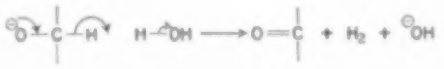
[35] R. Fittig and J. G. Spenzer, *Liebigs Ann.* **283**, 66, 80 (1894).
[36] F. Fichter and F. Sonneborn, *Ber. Dtsch. Chem. Ges.* **35**, 938 (1902).
[37] D. J. G. Ives and R. H. Kerlogue, *J. Chem. Soc.* 1362 (1940).
[38] L. N. Owen, private communication.

underwent fission is incompatible with the formation of a long chain fatty acid and acetic acid in approximately equimolar proportions.

With regard to "route B", it is known that aldehydes are readily converted by concentrated alkalis into acids.[39] The reaction may be represented as an attack by



hydroxyl ion to give either XIII or, by analogy with the Cannizzaro reaction,[40] the double charged species XIV, followed by transfer of a hydride ion to some acceptor. If the latter is water, then hydrogen is formed simultaneously and hydroxyl ion regenerated:



Similar transformations are probably involved in the conversion of primary alcohols into acids[44] on treatment with concentrated alkalis, and in related processes.

Attempts to demonstrate the formation of aldehydes during the alkali fission of ethylenic or β-hydroxy-acids have so far met with little success. No acetaldehyde (or acetone) could be entrained in a steam of nitrogen during the alkali fusion of crotonic and β-hydroxybutyric acid (acetoacetic and 3-oxononanoic acid gave small amounts of acetone and nonan-2-one respectively). However treatment of both acids with hot 40 per cent potassium hydroxide gave traces of acetaldehyde (acetoacetic and 3-oxononanoic acid again gave acetone and nonan-2-one respectively), and the fission of β-alkyl-$\alpha\beta$-ethylenic acids and β-alkyl-β-hydroxy acids to ketones under similar conditions is well authenticated.[41,42] The recent report that distillation of ethyl 2-methyl-2-benzyl-3-hydroxypentanoate in the presence of traces of alkali gives

[39] H. S. Fry and E. L. Schulze, *J. Amer. Chem. Soc.* **48**, 958 (1926); G. H. Hargreaves and L. N. Owen, *J. Chem. Soc.* 753 (1947).
[40] L. P. Hammett, *Physical Organic Chemistry*. McGraw-Hill, New York (1940).
[41] R. P. Linstead, *J. Chem. Soc.* 362 (1927).
[42] M. M. Schemjakin and I. A. Redkin, *J. Gen. Chem. U.S.S.R.* **11**, 1163 (1941).

propionaldehyde and ethyl 2-benzylpropionate is also relevant.[43] Although not conclusive, these considerations favour "route B" for the fission of β-hydroxy-acids.

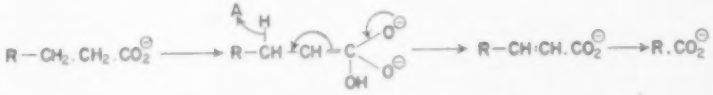
The overall yields of the saturated fatty acids formed on substantially complete reaction of the various ethylenic acids studied are summarized in Table 6 (acetic acid was not normally isolated). Small amounts of by-products were also detected, and their formation deserves comment.

TABLE 6. OVERALL YIELDS OF FISSION PRODUCTS

Starting material	Reaction conditions	Principal product	
		Acid	Yield (%)
Oleic	360°/60 min	palmitic	80–85
Petroselinic	360°/30 min	palmitic	78
$\alpha\beta$-Oleic	360°/60 min	palmitic	83
Undec-10-enoic	360°/30 min	nonanoic	80
Non-2-enoic	300°/5 min	heptanoic	~80

Even after prolonged fusion with alkali the product from oleic acid was not fully saturated. The residual unsaturated acids (ca. 5 mol %) were probably composed mainly of isomers in which the double bond had migrated into positions remote from the carboxyl group, and of unsaturated polymers. These by-products were less in evidence with alkali fusions of petroselinic and $\alpha\beta$-oleic acid.

A commonly encountered impurity (ca. 2–3 mol %) in the fusion products was the saturated acid with two carbon atoms fewer than the main product. Direct experiment with palmitic and capric acid showed that these impurities were formed by further reaction of the main products. Under more drastic conditions than those used in the present studies, γ-alkyl acids have been degraded to α-alkyl acids.[46] Pending a detailed examination of reactions of this type, they are tentatively regarded as proceeding by an initial slow dehydrogenation, involving the transfer of a hydride ion to an acceptor (A), followed by a rapid fission of the resulting $\alpha\beta$-ethylenic acid:



The first of these steps may well be reversible under suitable conditions. Thus it is conceivable that the 2-enoate intermediates in the fission of ethylenic acids might act as an acceptor of hydride ions, e.g. from XIII or XIV, leading to the saturated analogue of the starting material. The oleic acid fusion products contained traces (≯1%) of stearic acid, and Werber *et al.*[8] obtained 2–3% cyclohexanecarboxylic acid from the

[43] J. R. Hanley, H. S. Killam, R. D. Lanyon, S. MacKenzie, *J. Org. Chem.* **23**, 1461 (1958).
[44] J. Dumas and J. S. Stass, *Liebigs Ann.* **35**, 129 (1840); M. M. Guerbet, *Bull. Soc. Chim. Fr.* **11**, 164 (1912).,
[45] M. M. Guerbet, *Ann. Chim. Phys.* **27**, 67 (1902).
[46] E. L. Pelton and A. A. Holzschuh, U.S. Pat. 2425343, 2531363.

alkaline fission of cyclohexenecarboxylic acids. The formation of 5–10 per cent of octanoic acid in the alkali fusion of oct-2-enoic acid was noted by Hunter and Popják;[14] their starting material was contaminated with neopentyl alcohol which probably served as the hydrogen donor. Hydrogen transfers of the type under consideration appear to assume greater importance in the fission of diene and acetylenic acids (Part II).

Another possible side-reaction is the addition of a carbanion to a 2-enoate intermediate, in a reaction of the Michael type, to give products which can then undergo further transformations. The production of high boiling acids was observed in many alkali fusions, but these products were not investigated further.

Other materials detected chromatographically or spectrally in fusion products were traces of saturated acids, with three and five carbon atoms less than the starting material, dicarboxylic acids (azelaic and sebacic from oleic; sebacic and lower homologues from undec-10-enoic), and hydroxy-acids. Though not normally prominent, it is possible that side reactions leading to such by-products become significant under modified conditions. Thus Treibs and Rothe[47] have claimed that heating oleic acid with aqueous alkali in oxygen gave 9:10-dihydroxystearic acid and sebacic acid, and that undec-10-enoic acid under similar conditions gave azelaic acid. Again Jegerow[6] reported isolating 5- (or 6-) hydroxystearic acid after heating oleic acid with aqueous potassium hydroxide; the structure of his product is, however, doubtful as its m.p. was lower than those subsequently reported for the authentic hydroxystearic acids.[48]

Finally we wish to emphasize that, despite the variety of side reactions that have been observed, the products of Varrentrapp reactions carried out under favourable conditions can be readily purified by standard procedures.

EXPERIMENTAL

(M.p.s were determined on samples in capillary tubes.)

Analytical methods

Iodine values were determined by the method of Benham and Klee[49] using samples of 0·1–0·3 g. Authentic specimens of oleic, elaidic, petroselinic, octadec-2-enoic and undecylenic acid gave values within ±0·5 of the theoretical; methyl octadec-*trans*-10: *trans*-12-dienoate within ±2; β-elaeostearic and sorbic acid gave 90 and 60% respectively of the calculated values; palmitic and 10-hydroxystearic acid under similar conditions gave apparent iodine values of <0·2 and ca.1–3 respectively.

Infra-red light absorption spectra were determined on a Grubb–Parsons D.B. spectrometer. The proportions of (unconjugated) *cis* and *trans* ethylenic acids were determined by the intensity of the absorption maximum at 10·36 μ shown by the methyl esters in carbon disulphide solution (cf. [50]).

Ultra-violet light absorption spectra were determined on a Unicam Quartz Spectrophotometer, using ethanolic solutions. Estimations of the amounts of α,β-unsaturated acids were made from the intensity of absorption at 209 mμ of the derived methyl esters, correction being made for the background absorption by non-conjugated isomers and saturated esters (cf. [51]).

Acetic acid was estimated by steam distillation and titration, or, more accurately, by azeotropic distillation with benzene.[52] Other mono-acids were analysed by gas–liquid chromatography (G.L.C.) of their methyl esters in nitrogen, generally on silicone or Apiezon columns using a positive inlet pressure and either a katharometer or thermistor detector; adjacent members of the homologous

[47] W. Treibs and M. Rothe, *Chem. Ber.* **84,** 370 (1951).
[48] S. Bergstrom, *Acta Chem. Scand.* **6,** 1157 (1952).
[49] G. H. Benham and L. Klee, *J. Amer. Oil Chem. Soc.* **27,** 127 (1950).
[50] O. D. Shreve, M. R. Heether, H. B. Knight and D. Swern, *Analyt. Chem.* **22,** 1261 (1950).
[51] J. Cason and G. Sumrell, *J. Org. Chem.* **16,** 1181 (1951).
[52] S. T. Schicktanz, W. I. Steele and A. C. Blaisdell, *Industr. Engng. Chem.* (*Anal.*) **12,** 320 (1940).

series up to methyl stearate were readily separated. Quantitative analyses were made either by the "normalization procedure" or by means of an "internal standard" (e.g. methyl caprate or myristate); "correction factors" for different components of a mixture were determined with authentic mixtures of approximately the same composition.[53]

Dicarboxylic acids were analysed by paper chromatography in an all-glass cabinet (Shandon) maintained at constant temperature by immersion in a bin of sawdust. The paper (Whatman No 1) was irrigated with aqueous ammoniacal ethanol, and the spots were subsequently developed by spraying firstly with bromo-cresol green and then with lead acetate.[54] Good separations of dicarboxylic-acids from C_3 to C_{12} were achieved. Identifications were made by mixed chromatograms on the same sheet. Quantitative analyses were made by comparison chromatograms of the unknown and authentic mixtures. Model experiments showed that the linear relationship between spot area and log. (moles of acid), previously established for the lower aliphatic mono-carboxylic acids,[55] also applied to the dicarboxylic acids from C_4 to C_{11} with an accuracy of $\pm 5\%$ provided that (i) all spots were on the same sheet, (ii) the solution of acids applied to the paper was allowed to spread freely, and not evaporated during application, (iii) the concentration of each component in the solution was $>0{\cdot}05$ M, and (iv) the amounts of the acid in the spots being compared did not differ by a factor of $>$ca. 1·3. To conform with these requirements the sample was often separated in such a way as to concentrate the minor components, and the fractions analysed separately (see under "Oxidation" below). Components applied to the paper in solution $<0{\cdot}05$ M gave spots of different colours on development. Visual comparison of these spots with those obtained on the same sheet with equal volumes of standard solutions allowed quantitative estimates to be made with an accuracy of ± 10–15%.[56] It is possible that the dicarboxylic acids could be more conveniently analysed by G.L.C. of their methyl esters, a technique which has been developed since most of the above analyses were carried out.[57]

Starting materials

Commercial potassium hydroxide pellets ($<84{\cdot}5\%$ KOH) were used in all alkali fusions.

Nitrogen was freed from oxygen and dried.

All saturated mono-carboxylic acids were purified by fractional distillation of their methyl esters, and/or by crystallization, until G.L.C. of their methyl esters indicated purities $>99{\cdot}5\%$. Dicarboxylic acids were purified by fractional crystallization, and gave only one spot on a paper chromatogram.

The origin and properties of the unsaturated acids are indicated below:

Oleic acid. Olive oil (3·8 kg, B.P. grade) was hydrolysed,[58] and the fatty acids obtained were slowly cooled to 15°. The solid which separated was removed by centrifugation, and the residual liquid acids were purified firstly by means of their urea complexes,[59] and then by distillation of their methyl esters (prepared with $MeOH$–H_2SO_4) at 2·5 mm through a Stedman column (60 × 2 cm). Collection of the C_{18} fraction, hydrolysis and low temperature crystallization from acetone,[60] then gave oleic acid (265 g), m.p. 13·25–13·40°, n_D^{20} 1·4597 (Smith[60] gives m.p. 13·36° for the α-form, and Craig[61] gives n_D^{20} 1·4597) (Found: I.V., 89·4. Calc: I.V., 89·9). Spectrometric analyses (kindly carried out by the Paint Research Laboratory, Teddington) showed the linoleic acid content to be $<0{\cdot}5\%$. The methyl ester exhibited no light absorption maxima at 10·36 μ (absence of *trans*—CH:CH—) or 233 mμ (absence of conjugated diene), and gave one band on gas–liquid chromatography.

Ozonolysis, and chromatographic analysis of the resulting acids, revealed no mono- or di-acids greater than C_9 (absence of positional isomers of oleic acid cf. [62]); the detection of traces (ca. $0{\cdot}1\%$) of hexanoic and stearic acid suggests that the oleic acid contained traces of linoleic and stearic acid.

[53] A. I. M. Keulemans and C. G. Verver, *Gas Chromatography*. Reinhold, New York (1957).
[54] R. I. Chaftel, R. Munier and M. Marcheboeuf, *Bull. Soc. Chim. Biol.* **34**, 380 (1952); cf. H. Kalbe, *Z. Physiol. Chem.* **297**, 19 (1954).
[55] R. L. Reid and M. Lederer, *Biochem. J.* **50**, 60 (1952).
[56] R. J. Block, R. LeStrange and G. Zweig, *Paper Chromatography*. Academic Press, New York (1952).
[57] cf. A. T. James and J. Webb, *Biochem. J.* **66**, 515 (1957).
[58] H. B. Knight, E. F. Jordan, E. T. Roe and D. Swern, *Biochem. Prep.* **2**, 100 (1952).
[59] D. Swern and W. E. Parker, *J. Amer. Oil Chem. Soc.* **29**, 614 (1952).
[60] J. C. Smith, *J. Chem. Soc.* 974 (1939).
[61] B. M. Craig, *Canad. J. Chem.* **31**, 499 (1953).
[62] R. R. Allen and A. A. Kiess, *J. Amer. Oil Chem. Soc.* **32**, 400 (1955).

Elaidic acid. This was prepared by treating oleic acid with oxides of nitrogen.[62] It had m.p. 44·4–44·9° corr (lit.[64] m.p. 43–45°) (Found: I.V. 89·5. Calc.: 89·9). Ozonolysis gave no acids greater than C_9 (absence of positional isomers).

Using the above procedure no positional isomers could be detected even in the crude reaction mixture. However the widely used Bertram method,[65] involving stereomutation with catalytic amounts of selenium, was found to give up to 10% of positional isomers (Δ^8 and Δ^{10} with smaller amounts of Δ^7 and Δ^{12}) depending on the extent of the reaction and the purity of the selenium.

Petroselinic acid (cf.[66]). Hydrolysis of the seed oil (480 g) of *Ammi visnaga* (kindly supplied by Dr. J. H. Skellon), fractional distillation (Stedman, 60 × 2 cm) at 2 mm of the methyl esters of the resulting acids, and hydrolysis of the C_{18} fraction gave a mixture of acids. Separation of the solid and liquid acids by the lead salt technique,[8] and crystallization of the former from acetone, gave petroselinic acid (30 g), m.p. 29·5–29·7° (lit.[64] m.p. 30°) (Found: C, 76·6; H, 12·25%; I.V., 89·2. Calc. for $C_{18}H_{34}O_2$: C, 76·55; H, 12·15%; I.V., 89·9). It showed no infra-red light absorption at 10·36 μ (absence of *trans* —CH:CH—). Ozonolysis led to no mono-acids greater than C_{12} and no di-acids greater than C_6 (absence of positional isomers).

Octadec-2-enoic acid. This acid was prepared in 14% yield from stearic acid by Myers' method.[67] It had m.p. 58·0–58·5° corr (lit.[67] m.p. 58°) (Found: C, 76·6; H, 12·25%; I.V., 89·8. Calc. for $C_{18}H_{34}O_2$: C, 76·55; H, 12·15%; I.V., 89·9).

Esterification (CH_2N_2 or MeOH–H_2SO_4) gave the methyl ester, m.p. 34·4–35·2° (lit.[68] m.p. 34–35°) (Found: I.V., 86·0. Calc.: 85·6): λ_{max} (EtOH), 209 mμ (ε 14,500); λ_{max} (CS_2) 10·25 μ (ε 96·5) (conjug *trans* —CH:CH—).

Non-2-enoic acid. This acid, prepared by condensing heptaldehyde with malonic acid,[69] had b.p. 135–137°/5·5 mm, n_D^{22} 1·4598 (lit.[64] gives b.p. 130–132°/2 mm, n_D^{22} 1·4598). Esterification (MeOH–H_2SO_4) gave the methyl ester, b.p. 145°/85 mm, n_D^{20} 1·4443, end absorption at 209 mμ (ε, 9600), λ_{max} (liq film) 6·10 (conjugated CO_2Me) and 10·28 μ (conjugated *trans* —CH:CH—), which gave one peak on gas–liquid chromatography (on silicone the R_F was greater than that of other methyl-nonenoates and methyl nonanoate).

Undec-10-enoic acid. Commercial undecylenic acid (St. Just) was fractionally distilled (Stedman, 60 × 2 cm) at 7 mm, and then crystallized from light petroleum (b.p. 40–60°). The product had m.p. 25·1–25·4°, n_D^{25} 1·4471 (Ashton and Smith[70] give m.p. 25·5°; Jordan and Swern[71] give m.p. 24·3–24·5°) (Found: I.V., 137·4. Calc.: 137·5). The methyl ester (prepared with CH_2N_2) had no absorption at 10·36 μ (absence of *trans* —CH:CH—), and gave one band on gas–liquid chromatography.

Dodec-11-enoic acid. This acid was prepared by homologation of undec-10-enoic acid (cf. 72). It had m.p. 19·4–19·5°, n_D^{20} 1·4512 (lit.[72] m.p. 19·50°, n_D^{20} 1·4511) (Found: I.V., 126·0. Calc. 127·0). Infra-red and oxidation studies indicated the presence of ca. 1% of an isomeric acid.

Methyl 3-oxo-octadecanoate and 3-hydroxyoctadecanoic acid. The former was prepared from pure palmitic acid by Ställberg-Stenhagen's method[73] and had m.p. 49·6–50·0° (lit.[73] 48·7–49·2°) (Found: C, 73·1; H, 11·7. Calc. for $C_{19}H_{36}O_3$: C, 73·05; H, 11·6%). Reduction by Skogh's method,[74] and hydrolysis, gave 3-hydroxyoctadecanoic acid, m.p. 90·0–90·5° (lit.[73] 89·5–90·0°).

3-Hydroxybutyric acid. Reduction[75] of ethyl acetoacetate gave ethyl 3-hydroxybutyrate,

[62] C. H. Mack and W. G. Bickford, *J. Org. Chem.* **18**, 686 (1953).
[64] cf. A. W. Ralston, *Fatty Acids and their Derivatives*. John Wiley, New York (1948).
[65] S. H. Bertram, *Chem. Weekblad* **33**, 3 (1936); J. H. Skellon and J. W. Spence, *Chem. & Ind.* 302 (1953); D. Swern and J. T. Scanlon, *Biochem. Prep.* **3**, 118 (1953); D. K. Kolb and J. B. Brown, *J. Amer. Oil Chem. Soc.* **32**, 357 (1955).
[66] J. H. Skellon and J. W. Spence, *Chem. & Ind.* 75 (1954).
[67] G. S. Myers, *J. Amer. Chem. Soc.* **73**, 2100 (1951); cf. E. F. Jenny and C. A. Grob, *Helv. Chim. Acta* **36**, 1936 (1953).
[68] R. G. Sinclair, A. F. McKay, G. S. Myers and R. N. Jones, *J. Amer. Chem. Soc.* **74**, 2578 (1952).
[69] K. von Auwers, *Liebigs Ann.* **432**, 46 (1923); A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.* 2343 (1928).
[70] R. Ashton and J. C. Smith, *J. Chem. Soc.* 435 (1934).
[71] E. F. Jordan and D. Swern, *J. Amer. Chem. Soc.* **71**, 2377 (1949).
[72] C. G. Tomecko and R. Adams, *J. Amer. Chem. Soc.* **49**, 522 (1927); J. M. Rountree and J. C. Smith, *Chem. & Ind.* 190 (1954).
[73] S. Ställberg-Stenhagen, *Arkiv. Kemi* **20A**, No. 19 (1945).
[74] M. Skogh, *Acta Chem. Scand.* **6**, 809 (1952).
[75] K. Serck-Hanssen, S. Ställberg-Stenhagen and E. Stenhagen, *Arkiv. Kemi* **5**, 203 (1953).

b.p. 87–89°/20 mm, n_D^{17} 1·4208 (lit,[75] b.p. 76–77°/15 mm, n_D^{24} 1·422), λ_{max} 5·78 μ (—CO_2Et). Alkaline hydrolysis at 20° gave the hygroscopic acid.

3-Oxodecanoic and 3-oxobutyric acid. Methyl 3-oxodecanoate was prepared from pure octanoic acid by Ställberg-Stenhagen's method[72] and had b.p. 117–120°/2 mm, $n_D^{24\cdot5}$ 1·4371 (lit.[73] n_D^{20} 1·4393). The ester was hydrolysed at 20° with dilute potassium hydroxide.[76] The resulting solution was either treated with further potassium hydroxide to give the desired alkali concentration for fission studies, or, after neutralization of the excess alkali with dilute hydrochloric acid, freeze-dried to give the (hygroscopic) potassium salt which was used in alkali fusions. The potassium salt of 3-oxobutyric acid was similarly prepared from ethyl acetoacetate.[77]

Alkali fusions

In some preliminary studies oleic acid was heated with potassium hydroxide in an open nickel crucible at 340°. A soft tacky soap was formed. After about 15 min, this coagulated to a putty-like mass. On further heating the mass softened, and an exothermic reaction occurred with vigorous evolution of hydrogen. After the reaction had subsided, the residual dark solid was cooled. Isolation of the product gave palmitic acid in ca. 50% yield.

All subsequent fusions were carried out in a cylindrical nickel pot (internal dimensions; 5·7 × 3·4 cm) having a lid (Syndanio lined with nickel) fitted with nitrogen inlet and outlet ports, and a nickel stirrer (attached to a 50 r.p.m. shaft) and thermocouple well. The acid (usually ca. 3 g), and 3 parts by weight of potassium hydroxide, were placed in the pot which was then closed and flushed rapidly with nitrogen. The flow of nitrogen was reduced to ca. 4 ml/min, the mixture stirred, and the pot placed in a Wood's metal bath, preheated to ca. 60° above the required temperature. The bath was strongly heated with a Meker burner until the required temperature was attained (2–3 min), when the rate of heating was adjusted so that the bath temperature was constant throughout the experiment. (Separate studies showed that, for bath temperatures of 275–350°, the internal temperature of the pot rose to within ca. 15° of the bath temperature in ca. 5 min, and then remained approximately constant.) At the end of the desired reaction time, the metal bath was replaced by a water bath, thus quenching the reaction within 2–3 min. The contents of the pot were dissolved in water (150 cc/g of acid), and the solution was acidified and then extracted with light petroleum (b.p. 40–60°). The extract was dried and evaporated giving the acidic product (90–95 mol %). A portion was used for the iodine value determination and oxidation studies, and another, after esterification with methanolic sulphuric acid, for spectral studies and G.L.C. examination. Thorough extraction of the aqueous mother liquors with ether sometimes gave small amounts (<5%) of a material similar in composition to the main product, but containing traces of dicarboxylic acids.

Fusion of oleic acid with one part by weight of potassium hydroxide at 300°/30 min gave a product identical with that obtained using the standard proportion of alkali.

The majority of the results are summarized in the Tables. The following notes illustrate the characterization of some of the main fission products.

(i) Oleic acid (3·04 g) and potassium hydroxide (9·2 g) were heated at 360° for 60 min (cf. Table 2). Isolation gave a crude product (2·65 g) which was shown (G.L.C. of methyl esters) to contain ca. 5, 90 and 1 mol % of octadecenoic acids, palmitic acid and myristic acid respectively (Found: I.V., 5·8). Crystallization of the crude product from methanol gave palmitic acid, m.p. and mixed m.p. 62·5–62·8° corr.

(ii) Similarly alkali fusion of petroselinic acid (2·53 g) at 360° for 30 min (cf. Table 3) gave a crude product (2·7 g) (Found: I.V., 2·1). One crystallization from methanol gave palmitic acid, m.p. and mixed m.p. 62·0–62·5°.

(iii) Undec-10-enoic acid (2·696 g) and potassium hydroxide (8 g) were heated at 360° for 30 min. The product was cooled and dissolved in water. The solution was acidified and steam distilled, and the distillate was neutralized and evaporated. Analysis (cf. 52) of the residue by acidification with toluene-*p*-sulphonic acid and azeotropic distillation gave acetic acid (0·54 g), *p*-bromophenacyl ester, m.p. and mixed m.p. 83°. The long chain fatty acids (1·82 g) were isolated from the still residues and shown (G.L.C. of methyl esters) to contain 88% of nonanoic acid and 12% of undecenoic acids. The yields of acetic and nonanoic acid, based on the amount of undecenoic acid which underwent fission, were 67 and 74% respectively.

[76] cf. L. Breusch and H. Keskin, *Rev. Fac. Sci. Univ. Istanbul* **11A**, 24 (1946).
[77] cf. P. Karrer and C. H. Eugster, *Helv. Chim. Acta* **32**, 1934 (1949).

Alkali fusion of undec-10-enoic acid (21·1 g) at 360°/30 min, isolation and steam distillation of the crude product gave nonanoic acid (13·82 g, 75%) which was shown to be 99% pure. Extraction of the residues from the steam distillation gave high boiling acids (1·91 g).

(iv) Non-2-enoic acid (3·00 g) and KOH (9 g) were heated at 300° for 30 min. Isolation gave heptanoic acid; anilide, m.p. 69–70° (lit.[64] m.p. 71°).

(v) Methyl 3-oxo-octadecanoate (0·53 g) was heated with KOH (1·5 g). The bath temp was raised from 200–300° over 5 min and then kept at 300° for 30 min. Isolation gave a non-saponifiable product (0·11 g) and an acid fraction (0·24 g), which consisted mainly of palmitic acid (G.L.C. of methyl esters).

(vi) The potassium salt of 3-oxodecanoic acid (from 1·0 g of methyl ester) and KOH (3 g) were heated from 200° to 300° and kept at this temp for 1 hr. A liquid (0·10 g, 13%) which condensed in a cold trap in the nitrogen outlet line was identified as nonan-2-one (semicarbazone, m.p. and mixed m.p. 120°). Isolation of the acidic product gave octanoic acid (0·49 g, 63%); *p*-bromophenacyl ester, m.p. and mixed m.p. 66°. A trace of hexanoic acid was also detected (G.L.C. of methyl esters).

Alkali fusion of the potassium salt of acetoacetic acid at 300°/1 hr gave acetone (2:4-dinitrophenylhydrazone, 5% overall; in a control experiment acetone was recovered in 50% yield).

Fissions in aqueous alkali

Solutions of the $\alpha\beta$-unsaturated, β-hydroxy, or β-oxo-acids in 40% KOH were heated at 130° in hard glass flasks. A stream of nitrogen was passed through the reaction mixture, to entrain any volatile products, and then into aqueous 2:4-dinitrophenylhydrazine sulphate, dimedone reagent, or a cold trap.

Acetaldehyde (ca. 1%) from crotonic and β-hydroxybutyric acid was identified as the 2:4-dinitrophenylhydrazone and dimedone derivative, acetone from 3-oxobutyric acid as the 2:4-dinitrophenylhydrazone, and octan-2-one from 3-oxodecanoic acid as the semicarbazone (and by G.L.C.).

Oxidations of unsaturated acids

Oxidative fission of unsaturated fatty acids, and their derivatives, is usually accompanied by undesirable side reactions (cf.[78]). After a study of various methods, the following improvement of a procedure by Klenk and Bongard[79] was adopted as the best available at the time the present work was commenced.

A stream of ozonized oxygen (3–5% O_3) was slowly bubbled through a cooled (0°) solution of the fatty acid or mixture (ca. 1 g) in glacial acetic acid (30 cc) and methyl acetate (10 cc) until ca. 20% excess of ozone had been introduced. Most of the solvent was then evaporated by warming (steam-bath) the mixture under reduced pressure in an all glass apparatus. To the residue, glacial acetic acid (40 cc) and then 30% hydrogen peroxide (5 cc, unstabilized) were added. The solution was kept at ca. 35° for 48 hr and then poured into water (200 cc). The mixture was extracted with light petroleum (b.p. 40–60°) (100 cc), and the extract washed once with warm water (20 cc). The petroleum solution was dried and evaporated. The residual mono-carboxylic acids were esterified ($MeOH–H_2SO_4$) and the methyl esters examined by G.L.C. The aqueous mother liquors and washings were combined and concentrated (to 50 cc) under reduced pressure. Water (100 cc) was added and the concentration repeated. The residual solution (50 cc) was extracted once with chloroform (50 cc), and the two phases evaporated to dryness under reduced pressure. The residues were crystallized from small volumes of water (or alcohol) and chloroform respectively, and the two mother liquors evaporated to dryness. The four fractions, comprising the dicarboxylic acids, were dissolved in ethanol, and the solutions analysed by paper chromatography. By the preliminary separation it was possible to insure that the concentrations of the minor products exceeded the limiting value of 0·05 M in the solutions being analysed, and that the concentrations of the various components in any one chromatogram did not differ by a factor of >10–20, as recommended by Bighi and Trabanelli.[80]

Oxidation of pure oleic, elaidic, petroselinic, undec-10-enoic and dodec-11-enoic acid by the above

[78] P. H. Begemann, J. G. Keppler and H. A. Boekenoogen, *Rec. Trav. Chim.* **69**, 439 (1950); J. G. Keppler, *Ibid.* **76**, 49 (1957).
[79] E. Klenk and W. Bongard, *Z. Physiol. Chem.* **290**, 181 (1952).
[80] C. Bighi and G. Tranbanelli, *Ann. Chim.* (*Rome*) **45**, 109 (1955).

procedure gave the products summarized in Table 7. The formation of lower homologues of the principal products was very similar in both the mono- and the di-carboxylic acid fractions. These by-products, which totalled ca. 5–7 mol %, were composed mainly of the homologues with one or two carbon atoms fewer than the principal products. The absence of any higher homologues excludes the possibility that the starting materials were contaminated with positional isomers.

The yields of dicarboxylic acids given in Tables 1–6 are uncorrected for side reactions of the above type, which affect the principal products only slightly. The general conclusions concerning the approximate proportions of isomeric ethylenic acids in fusion products are therefore valid. Only where an acid was found as a small proportion of a longer chain homologue is there reason to believe

TABLE 7. OXIDATION OF ETHYLENIC ACIDS
Yields of mono- (M) and di- (D) carboxylic acids in mol %

Oleic		Elaidic		Petroselinic		Undec-10-enoic	Dodec-11-enoic*
M	*D*	*M*	*D*	*M*	*D*	*D*	*D*
C_9 71·8	C_9 69·3	C_9 69·5	C_9 68·2	C_{12} 70·2	C_6 55·9	C_{10} 70·6	C_{11} 55·6
C_8 2·7	C_8 2·1	C_8 3·9	C_8 2·1	C_{11} 4·9	C_5 3·9	C_9 0·9	C_{10} 0·6
C_7 0·4	C_7 1·0	C_7 0·2	C_7 1·2	C_{10} 0·2	C_4 0·3	C_8 0·8	C_9 1·2
C_6 0·2	C_6 0·4	C_6	C_6 0·2			C_7 0·2	C_8 0·0
C_5	C_5 0·5	C_5	C_5 0·3			C_6 0·5	C_7 0·1
C_4	C_4 0·7	C_4	C_4 0·6			C_5 0·7	C_6 0·2
						C_4 1·3	C_5 0·2
							C_4 0·3
75·1	74·0	73·6	72·6	75·3	60·1	75·0	58·2

* Contains ca. 1% of an isomer.

that it may be mainly an artefact, due to side reactions of the above type, rather than an oxidation product of the corresponding ethylenic acid. Values likely to be seriously affected in this way are given in the tables in brackets [ ]. Though the detection after oxidation of a small amount of a mono- or di-carboxylic acid shorter than the main product does not necessarily indicate the presence of a particular isomeric ethylenic acid, the detection of the complementary di- or mono-carboxylic acid longer than the main product provides convincing evidence. Thus after alkali fusion of oleic acid at 300°/30 min, the presence of the Δ^6, Δ^7 and Δ^8 isomers, indicated by the formation of the C_6, C_7 and C_8 dicarboxylic acids on oxidation (Table 1), is confirmed by the simultaneous formation of the C_{10}, C_{11} and C_{12} monocarboxylic acids.

Another limitation of the above procedure for the analysis of complex mixtures of isomeric ethylenic acids must also be considered. The separation of the mono- and di-carboxylic acids in the oxidation products by extraction of the former with petroleum ether is unsatisfactory in the presence of long chain dicarboxylic acids;[81] thus the recovery of thapsic acid was shown to be only 50%. It is also significant that the yield of undecanedioic acid from dodec-11-enoic acid was appreciably lower than that of sebacic or azelaic acid from undec-10-enoic and oleic acid respectively (Table 7). Moreover the chromatographic procedure used in the present studies was unsuitable for the analysis of dicarboxylic acids beyond C_{12}. Any ethylenic acids with a double bond more remote than the Δ^{12} position therefore escaped detection by the above procedure, and low figures were obtained for the amounts of Δ^{11} and Δ^{12} compounds. Only some of the results with oleic acid are likely to have been influenced by these factors. Values for dicarboxylic acids which are regarded as low are quoted in Tables 1 and 2 in parentheses ( ). In one experiment on the alkali fusion of oleic acid at 360°/60 min,

[81] cf. V. Zbinovsky, *Analyt. Chem.* **27**, 764 (1955).

the glacial acetic acid solution of the oxidation products was diluted with half the normal volume of water, and the analysis then carried out in the usual way. As expected, a big loss of the monocarboxylic acids was incurred, but the yield of the long chain dicarboxylic acids increased markedly (Table 2).

Carbon and hydrogen determinations were carried out in the microanalytical laboratory (Miss J. Cuckney), and ultra-violet (Mrs. A. I. Boston) and infra-red measurements (Mr. R. L. Erskine) in the spectrographic laboratory of this department.

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ORGANIC REACTIONS IN STRONG ALKALIS—II[1]

FISSION OF DI-ETHYLENIC AND ACETYLENIC ACIDS

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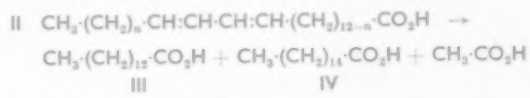
Abstract—Linoleic and stearolic acid give myristic acid, together with small amounts of palmitic acid, on treatment with molten potassium hydroxide. These, and similar reactions of other acetylenic acids, are discussed.

As a continuation of the studies on mono-ethylenic acids described in the previous paper,[1] the alkali fusion of representative acids of the diene and acetylene series was examined.

The isomerization of linoleic acid (I) in hot dilute alkalis to a mixture of octadeca-9:11- and octadeca-10:12-dienoic acids (II; $n = 4$ and 5) is well known, and forms the basis of a widely used method of fat analysis.[2–5] Under the more drastic conditions of alkali fusion the conjugated dienes, which are doubtless formed initially, can then react further both by polymerization[6] and by fission. The latter process, by analogy with the conversion of oleic into palmitic acid (IV),[1] might be expected to give myristic acid (III) with loss of four carbon atoms. Kirschenbauer[7] has stated that such a



transformation occurs during the alkali fusion of mixtures of fatty acids containing linoleic acid, but no experimental data have been published. From methyl linoleate Toyama and Iwata[8] obtained a solid product which they believed to consist mainly of palmitic acid and conjugated isomers of linoleic acid.

In our experience alkali fusion of linoleic acid gave mainly myristic acid (60 per cent) together with small amounts of palmitic acid (ca. 5 per cent). (The starting material contained only traces of oleic acid, and therefore the possibility that the palmitic acid observed was an artefact can be excluded.) Acetic acid, but no butyric, was also detected. The reaction was more rapid than that of oleic acid, but the yield of fission product was lower owing to the simultaneous occurrence of decomposition and polymerization.

[1] Part I: R. G. Ackman, Sir Patrick Linstead, B. J. Wakefield and B. C. L. Weedon, *Tetrahedron* **8**, 221 (1960).
[2] A. W. Ralston, *Fatty Acids and their Derivatives*. John Wiley, New York (1948).
[3] P. L. Nichols, S. F. Herb and R. W. Riemenschneider, *J. Amer. Chem. Soc.* **73**, 247 (1951).
[4] J. E. Jackson, R. F. Paschke, W. Tolberg, H. M. Boyd and D. H. Wheeler, *J. Amer. Oil Chem. Soc.* **29**, 229 (1952).
[5] J. J. A. Blekkingh, H. J. J. Janssen and J. G. Keppler, *Rec. Trav. Chim.* **76**, 42 (1957).
[6] cf. R. F. Paschke, J. E. Jackson and D. H. Wheeler, *Industr. Engng. Chem.* **44**, 1113 (1952).
[7] H. G. Kirschenbauer, U.S.P. 2682549; *Chem. Abstr.* **48**, 11819 (1954).
[8] Y. Toyama and Y. Iwata, *Res. Rept. Nagoya Ind. Sci. Res. Inst.* No. 8, 48 (1955); *Chem. Abstr.* **50**, 12814 (1956); *J. Amer. Oil Chem. Soc.* **33**, 375 (1956).

Information on the course of the fission reaction was sought by examination of the products formed under different conditions (Table 1). Although the competing reactions complicate the detailed interpretation of the results, a number of general conclusions can be drawn. By gas–liquid chromatography of their methyl esters, and those of the mono-carboxylic acids formed on oxidation, all products of incomplete

TABLE 1. ALKALI FUSION OF LINOLEIC ACID (30 min)

		245°[a]	280°[b]	300°	360°[c]
I.V. of product		115	66	16	8
Apparent loss of octadecadienoic acids[d]		38	66	92	97
Ultra-violet light absorption[e]		231(640)	230(310)	240(36)	—
Relative proportions (%) of C_{18} and lower acids	C_{18}	72	15	1·0	0
	C_{10}	3	5	12·4	6·7
	C_{14}	25	79	82·8	91·3
	C_{12}	0	1	1·4	1·9
Yield of myristic acid (mol %)		—	44	54	60
Proportion (%) of C_{16} : C_{14} acids before (and after) ozonolysis		12(25)	6(23)	15(16)	7(6)

[a] Ozonolysis of the product gave the C_{11} to C_4 dicarboxylic acids in >1·2, 5·1, 17·0, 2·2, 1·6, 1·4, 1·9 and 7·5 mol % overall yield respectively from linoleic acid (total yield based on residual octadecadienoic acids, ca. 60%), and the C_5 to C_{16} monocarboxylic acids.

[b] Ozonolysis of the product gave the C_{16} to C_3 dicarboxylic acids in 3·1, 4·1, 1·0, 1·7, 2·0 and 3·1 mol % overall yield respectively from linoleic acid and the C_6 to C_{16} monocarboxylic acids.

[c] 60 min.

[d] Calculated from I.V. of product without allowance for the formation of unsaturated polymers.

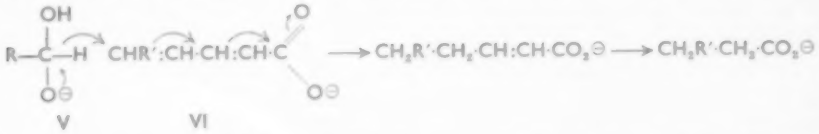
[e] λ_{max} in mμ; $E^{1\%}_{1cm}$ in parentheses.

reaction were found to contain myristic, palmitic and unsaturated C_{18}-acids. The loss of unsaturation, as shown by the iodine values of the products, was greater than could be accounted for by the amount of myristic acid detected; this discrepancy can be attributed to polymerization and other side reactions. Those products which retained large amounts of unsaturated acids exhibited light absorption maxima at ca. 230 mμ with intensities indicating that most of the residual unsaturation was present as conjugated dienes (cf. 3, 4). From the relative intensities of the infra-red light absorption maxima in the 10·0–10·6 μ region it was concluded that the dienes were predominantly the *trans*:*trans* isomers, with some *cis*:*trans* forms, and that small amounts of unconjugated (*trans*-) double bonds were also present (cf. 4). Oxidation gave mixtures in which the C_6 to C_{16} mono-carboxylic acids and the C_3 to C_{11} dicarboxylic acids were detected, indicating that the diene system had migrated in both directions

along the chain. Although unconjugated isomers of linoleic acid are not produced under mild conditions,[5] the initial rearrangement to conjugated dienes in molten alkali (involving proton removal at position 11) is apparently accompanied by the formation of some octadeca-8:12- and octadeca-9:13-dienoic acids (by proton removal at the less reactive positions 8 and 13), since oxidation of the product from the mildest alkali fusion studied gave unusually large amounts of succinic acid.

The formation of myristic acid can be attributed both to fission of a 2:4-dienoate (VI), resulting from migration of the diene system into conjugation with the carboxylate group, and to successive fissions of 2-enoate intermediates arising from the conjugation of individual double bonds with the oxygen function.

The various steps proposed above are explicable by obvious extensions of the mechanisms discussed in the previous paper[1] for the reaction of mono-ethylenic acids. It was suggested there that fission involved a hydride ion transfer from an intermediate of the type V. In the reaction now under consideration it seems plausible that a 2:4-dienoate (VI) can act as an acceptor in such a transfer. Under the conditions employed, the resulting octadecenoate would rapidly give a mixture of isomers, consisting mainly of the $\alpha\beta$- and $\beta\gamma$-compounds, and then undergo fission.[1] The formation of palmitic acid from linoleic acid can be satisfactorily explained in this way. Evidence for the presence of the octadec-2- and octadec-3-enoate intermediates in the products of incomplete reaction was provided by ozonolysis. This gave ad-



V VI

ditional quantities of palmitic acid (relative to myristic acid), and small amounts of pentadecanoic acid (absent from the fusion products themselves). Lower homologous acids from C_6 to C_{12} were produced simultaneously from the various unsaturated acids, and their polymers, also present.

The reaction products of low iodine value had ultra-violet light absorption maxima at different wavelengths from those of conjugated isomers of linoleic acid, and it is probable that polymers accounted for much of the residual unsaturation. These products also contained small amounts (ca. 1–2%) of lauric acid (a degradation product of myristic acid) and traces of the C_6 to C_{11} and the C_{13} monobasic acids. These latter impurities can be attributed to oxidations of the type discussed in Part III. The occurrence of other side reactions was not investigated.

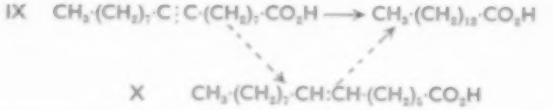
In agreement with the above conclusion, alkali fusion of sorbic acid (VI, R′ = Me) gave acetic acid (1·6 moles) and 2·5 per cent of butyric acid (*p*-bromophenacyl ester). Recently Lukeš and Hofman[9] reported that alkali fusion of 6:6-diallylhexanoic acid (VII) gave di-n-propylacetic acid (VIII) and acetic acid.

$$\underset{\text{VII}}{(CH_2{:}CH{\cdot}CH_2)_2CH{\cdot}(CH_2)_4{\cdot}CO_2H} \longrightarrow \underset{\text{VIII}}{(CH_3{\cdot}CH_2{\cdot}CH_2)_2CH{\cdot}CO_2H}$$

That alkali fusion of the acetylenic analogues of unsaturated fatty acids also leads to saturated products with loss of four carbon atoms was demonstrated by Marasse[10]

[9] R. Lukeš and J. Hofman, *Chem. Listy* **52**, 1747 (1958).
[10] S. Marasse, *Ber. Dtsch. Chem. Ges.* **2**, 359 (1869).

and Bodenstein.[11] The conversion of stearolic acid (IX) into myristic (III) and acetic acid was believed to proceed by the initial formation of hexadec-6-enoic acid (X). However fission of an intermediate of this type would not occur rapidly under the conditions employed (210–300°; cf. fission of oleic and petroselinic acid[1]). Moreover the extensive studies which have since been carried out on the prototropic rearrangements of acetylenes make such a reaction sequence extremely improbable. In alkaline



IX $CH_3\cdot(CH_2)_7\cdot C{:}C\cdot(CH_2)_7\cdot CO_2H \longrightarrow CH_3\cdot(CH_2)_{12}\cdot CO_2H$ III

X $CH_3\cdot(CH_2)_7\cdot CH{:}CH\cdot(CH_2)_6\cdot CO_2H$

solution hex-4-ynoic (XI, R = Me) and pent-4-ynoic acid (XI, R = H) isomerize to sorbic (XII, R = Me) and penta-2:4-dienoic acid (XII, R = H) respectively, and other ω-acetylenic acids (XIII) are converted into their methylacetylenyl analogues

XI $R\cdot C{:}C\cdot CH_2\cdot CH_2\cdot CO_2H \longrightarrow R\cdot CH{:}CH\cdot CH{:}CH\cdot CO_2H$ XII

XIII $HC{:}C\cdot(CH_2)_n\cdot CO_2H \longrightarrow Me\cdot C{:}C\cdot(CH_2)_{n-1}\cdot CO_2H$ XIV

(XIV).[12–14] All these rearrangements are believed to involve allenic intermediates and buta-2:3-dienoic acid has been isolated as the initial product from the reaction of but-3-ynoic acid (XIII, $n = 1$).[14] It might therefore be expected that, on alkali fusion of an acetylenic acid, the triple bond would migrate along the carbon chain by a sequence of reversible acetylene–allene–acetylene rearrangements which may be represented:

$$-C{:}C\cdot CH_2- \rightleftharpoons -CH{:}C{:}CH- \rightleftharpoons -CH_2\cdot C{:}C-$$

On reaching the Δ^4 position, formation of a 2:4-dienoate, an intermediate of the type postulated in the reaction of linoleic acid, would then precede fission. Our findings agree well with these expectations.

Alkali fusion of stearolic acid gave myristic acid (57 per cent) containing a small amount of a C_{16}-acid. This by-product was not destroyed by oxidation, and was therefore palmitic acid and not the hexadec-6-enoic acid reported by Bodenstein. As was to be expected if a common intermediate is involved, the proportion of palmitic to myristic acid was very similar to that obtained from the fission of linoleic acid under comparable conditions. Comparison of the loss of unsaturation, determined by the hydrogen numbers of the products, with the amounts of myristic acid formed, again showed that appreciable polymerization had occurred. Spectral examination of products of incomplete reaction revealed bands (230 mμ, 10·03, 10·15, 10·36 and 10·55 μ) indicating the presence of small amounts (<5 per cent) of conjugated dienes and unconjugated double bonds; a very weak band (5·09 μ) possibly due to traces of allenes was also observed. The residual C_{18}-acids were therefore mainly acetylenic, in accord with previous findings on the equilibria between acetylenes and allenes.[15] The dicarboxylic acids detected after oxidation demonstrated that the triple bond, like the double bond in ethylenic acids, migrates in both directions by a sequence of reversible rearrangements before fission occurs.

[11] M. Bodenstein, *Ber. Dtsch. Chem. Ges.* **27**, 3397 (1894).
[12] F. Krafft, *Ber. Dtsch. Chem. Ges.* **29**, 2232 (1896).
[13] E. Stenhagen, *Arkiv Kemi* **1**, 99 (1949).
[14] G. Eglinton, E. R. H. Jones, G. H. Mansfield and M. C. Whiting, *J. Chem. Soc.* 3197 (1954); E. R. H. Jones, G. H. Whitham and M. C. Whiting, *Ibid.* 3201 (1954).
[15] T. L. Jacobs, R. Akawie and R. G. Cooper, *J. Amer. Chem. Soc.* **73**, 1273 (1951).

TABLE 2. ALKALI FUSION OF STEAROLIC ACID

		245°/90 min[a]	300°/30 min	360°/30 min	360°/60 min
Relative proportions (%) of C_{18} and lower acids	C_{18}	73	4	—	2
	C_{16}	1·4	10	6	8
	C_{14}	25·6	86	91	89
	C_{12}	0	0	2	1
Yield of myristic acid (mol %)		19	—	51	~55

[a] Ozonolysis gave the C_{12} to C_4 dicarboxylic acids in 0·4, 1·9, 6·4, 13·9, 5·9, 1·4, 1·3, 0·6 and 1·0 mol % yield from stearolic acid (total yield of dicarboxylic acids based on the residual octadecynoic acids, ca. 50%). The methyl esters of the fusion product had λ_{max} 210 and 233 mμ, $E^{1\%}_{1cm}$ 50 and 80 respectively; hydrogenation number 211, equivalent to an I.V. of 120.

TABLE 3. ALKALI FUSION OF UNDEC-10-YNOIC ACID

	220°/30 min[a]	280°/15 min[b]	300°/60 min	300°/60 min	300°/60 min
Wt. ratio of alkali : acid	3 : 1	3 : 1	3 : 1	20 : 1	70 : 1
Relative proportions (%) of C_{11} and lower acids: C_{11}	99	87	0	0	0
C_9	trace	trace	29	21	17
C_7	1	13	71	79	83
Yield of heptanoic acid (mol %)	—	—	26	22	12
Yield of nonanoic acid (mol %)	—	—	9	5	2
Proportion (%) of C_9 : C_7 acids	—	—	35	23	17

[a] In a mixture (1 : 1) of NaOH and KOH. Hydrogenation no. of product = 168.

[b] Ozonolysis of product (hydrog. no. = 158; λ_{max} 230 mμ, $E^{1\%}_{1cm}$ = 110) gave the C_{10} to C_2 dicarboxylic acids, and the C_9 to C_5 monocarboxylic acids (proportion of C_9 : C_7 = 16%).

Alkali fusion of undec-10-ynoic acid (XIII, $n = 8$) was accompanied by extensive polymerization, but fission giving heptanoic acid (12–26%) was detected (Table 3). It is of interest that the formation of the by-product with loss of only two carbon atoms was more prominent in the C_{11} than the C_{18} series. Moreover, as required by the explanation offered above for this side reaction, the proportion of nonanoic to heptanoic acid fell with increasing dilution of the reaction mixture. Undec-9-ynoic acid also gave heptanoic (20–30%) and nonanoic acid (3–6%) on alkali fusion (300°/30 min), but trideca-6:12-diynoic acid polymerized completely (300°/60 min). Alkali

fusion (300°/30 min) of dodec-6-ynedioic acid (XV) gave suberic acid in 60 per cent yield and only 1 per cent of sebacic acid.

XV $HO_2C{\cdot}(CH_2)_4{\cdot}C{:}C{\cdot}(CH_2)_4{\cdot}CO_2H \longrightarrow HO_2C{\cdot}(CH_2)_6{\cdot}CO_2H$

The suppression of the side reaction in this example may be due to enhanced repulsion of the intermediates resulting from their increased negative charges.

The schemes discussed above for the fission of acetylenic fatty acids will not apply to the $\alpha\beta$- and $\beta\gamma$-acetylenic compounds. These are known to decompose in strong

XVI $CH_3{\cdot}(CH_2)_6{\cdot}C{:}C{\cdot}CO_2H \longrightarrow CH_3{\cdot}(CH_2)_6{\cdot}CO_2H$

alkalis, probably by initial hydration to a β-keto-acid.[14] As expected, alkali fusion (300°/10 min) of dec-2-ynoic acid (XVI) gave octanoic acid in low yield, traces of hexanoic acid and nonan-2-one (semicarbazone), and much non-saponifiable high boiling material. This result lends considerable support to the view that β-keto-acids are not key intermediates in the fission stage of the Varrentrapp reaction.[1]

EXPERIMENTAL

The general methods and analytical techniques used were those described in the experimental section to Part I.[1] Acetic and butyric acid were analysed by azeotropic distillation.[16]

Starting materials

Linoleic acid. The authors thank Dr. A. H. Hosking for a generous supply of methyl linoleate which had been prepared from the α-tetrabromide of natural linoleic acid. It had $n_D^{22.5}$ 1·4621; λ_{max} 228 mμ, $E_{1\,cm}^{1\%} = 42$ (ca. 3% of conjugated diene); 10·16 μ (trace of conjugated *cis*:*trans* diene); 10·36 μ (ca. 3% unconjugated *trans* double bond). Only one band was obtained on G.L.C. (silicone).

A solution of potassium hydroxide (10% excess) in methanol (10 vol) was added slowly (ca. 1 cc/10 min) to a boiling solution of methyl linoleate in methanol (15 min) in an atmosphere of nitrogen. The mixture was boiled for a further 15 min, cooled, poured into water, extracted with ether, and then acidified with 2 N H_2SO_4. Isolation of the product with ether gave linoleic acid.

Ozonolysis of linoleic acid gave mixtures of mono- and di-carboxylic acids in ca. 70% yield. The mono-carboxylic acid fraction consisted almost entirely of hexanoic acid, but contained ca. 0·2 mol % of octanoic and nonanoic acid (derived from oleic acid impurity). The dicarboxylic acid fraction consisted mainly of azelaic acid but also contained 2·2, 0·2 and 0·9 mol % of suberic, pimelic and succinic acid respectively; malonic acid was also detected qualitatively.

Stearolic acid. This was prepared from oleic acid[17] and had m.p. 47·5–48·5° (lit.[17] m.p. 46–46·5°), hydrogenation number, 142 (calc. 140). Ozonolysis gave nonanoic acid, which contained traces of octanoic and heptanoic acid (0·5 and 0·1 mol % respectively), and azelaic acid (86%) which was contaminated with 1·3, 1·4, 0·1, 0·3 and 0·4 mol % of suberic, pimelic, adipic, glutaric and succinic acid respectively.

Undec-10-ynoic acid. This was prepared[18] from undec-10-enoic acid and had m.p. 42·7–43·0° (lit.[2] m.p. 42·7–42·9°), λ_{max} (CCl_4) 3·04 (—C≡C—H) and 4·70 μ (C≡C). Its methyl ester gave only one band on G.L.C. and had b.p. 126–130°/12 mm, n_D^{22} 1·4460, λ_{max} 3·05 and 4·70 μ.

Undec-9-ynoic acid. This was prepared[18] from undec-10-enoic acid and had m.p. 59·0–59·5° (lit.[8] m.p. 59·5°). Its methyl ester gave only one band on G.L.C. and had b.p. 173–175°/100 mm, n_D^{20} 1·4514; it exhibited no light absorption at 3·04 μ (absence of —C:C—H).

Dodec-6-ynedioic and tridec-6:12-diynoic acid. The samples used were those previously described.[19]

Dec-2-ynoic acid. Carboxylation of the Grignard reagent of dec-1-yne gave the acid, b.p. 116–118°/0·9 mm, n_D^{19} 1·4546 (lit.[20] b.p. 164–168°/20 mm). Its methyl ester had b.p. 125°/17 mm (lit.[17]

[16] S. T. Schicktanz, W. I. Steele and A. C. Blaisdell, *Industr. Engng. Chem.* (*Anal.*) **12**, 320 (1940).
[17] H. Adkins and R. E. Burks, *Org. Synth.* **27**, 76 (1947).
[18] N. A. Khan, *Org. Synth.* **32**, 104 (1952); cf. L. Crombie and A. G. Jacklin, *J. Chem. Soc.* 1622 (1957).
[19] B. W. Baker, R. P. Linstead and B. C. L. Weedon, *J. Chem. Soc.* 2218 (1955).
[20] C. Moureu and R. Delange, *C. R. Acad. Sci., Paris* **136**, 552 (1903).

b.p. 133–135°/21 mm), n_D^{19} 1·4419, λ_{max} 4·45 μ (C≡C); the ultra-violet light absorption spectrum showed only end absorption, $E_{1\,cm}^{1\%}$ (208 mμ) = 300; G.L.C. indicated the presence of a trace of an impurity (<1%).

Alkali fusions

The majority of the results are summarized in the Tables. The following examples illustrate the isolation of some main reaction products.

(i) Linoleic acid (from 3·0 g of methyl ester) and KOH (9·0 g) were heated at 360° for 30 min (cf. Table 1). The crude acid product (ca. 75%) was isolated in the usual way[1] and had m.p. 50–51°. Crystallization from methanol gave myristic acid, m.p. and mixed m.p. 53·5–54°.

(ii) Stearolic acid (2·24 g) and KOH (7·0 g) were heated at 360° for 30 min (cf. Table 2). The crude acid product (1·54 g) was isolated and esterified (MeOH–H_2SO_4). Distillation gave a liquid, b.p. 100–110°/1 mm, which was shown by G.L.C. to contain >95% methyl myristate. Hydrolysis gave a solid m.p. 50–51°. Crystallization from light petroleum (b.p. 40–60°) gave myristic acid, m.p. and mixed m.p., 53·7–54·2°.

(iii) Dec-6-ynedioic acid (2·9 g) and KOH (9·0 g) were heated at 330° for 30 min. The mixture was cooled and dissolved in water. The solution was acidified and extracted thoroughly with ether. The extract was evaporated, and the residue esterified (MeOH–H_2SO_4). Analysis of the product by G.L.C. revealed methyl suberate and sebacate formed in 60% and 1% yield respectively. Distillation gave methyl suberate, b.p. 105–110°/2 mm, which was shown by G.L.C. to contain only traces of impurities. Hydrolysis, and crystallization from water, gave suberic acid, m.p. and mixed m.p. 144°.

Hydrogen numbers were determined in the microanalytical laboratory (Miss J. Cuckney), and ultra-violet (Mrs. A. I. Boston) and infra-red measurements (Mr. R. L. Erskine) in the spectrographic laboratory of this department.

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ORGANIC REACTIONS IN STRONG ALKALIS—III*

FISSION OF KETO- AND HYDROXY-ACIDS

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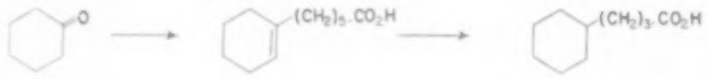
Abstract—Studies with suitable fatty acid derivatives have clarified many of the reactions of alcohols and ketones in concentrated alkalis.

Secondary alcohols are dehydrogenated to ketones which then yield acids by hydrolysis of the C—C bonds adjacent to the carbonyl group. Various side reactions are reported and discussed.

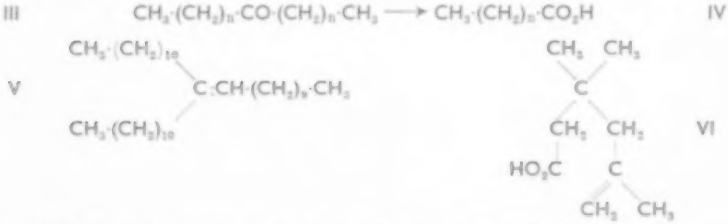
A mechanism is proposed for the fission of ricinoleic acid in concentrated alkalis.

A VARIETY of reactions has been reported for aliphatic and alicyclic ketones on alkali fusion. With camphor and fenchone Wallach noted the formation of acids by hydrolysis of a carbon-carbon bond adjacent to the carbonyl group.[1] A similar reaction with acetone, leading to acetic acid and methane, was subsequently described by Fry and Schulze.[2] With other ketones products have been isolated which suggest that alternative processes can accompany, or even largely replace, simple hydrolysis. Thus cyclohexanone, and its 2-allyl derivative, can give mainly 6-cyclohexenyl-



I II

hexanoic acid (I), or, by a further reaction of the Varrentrapp type, 4-cyclohexylbutyric acid (II),[3,4] and fission of laurone (III, n = 10) to lauric acid (IV, n = 10)



is accompanied by the formation of an olefin, probably (V).[5] A similar reaction is possibly involved in the conversion of isophorone into an acid regarded as VI.[6] The claim that palmitic acid (IV, n = 14) as well as stearic acid (IV, n = 16) is produced from stearone (III, n = 16) implies a further mode of reaction,[7] unless the former product is regarded as an artefact.

* Part II: *Tetrahedron* **8**, 239 (1960).

[1] O. Wallach and M. Behnke, *Liebigs Ann.* **369**, 98 (1909); cf. 8.
[2] H. S. Fry and E. L. Schulze, *J. Amer. Chem. Soc.* **48**, 958 (1926).
[3] T. L. Cairns, R. M. Joyce and R. S. Schreiber, *J. Amer. Chem. Soc.* **70**, 1689 (1948).
[4] E. L. Pelton, C. J. Starnes and S. A. Shrader, *J. Amer. Chem. Soc.* **72**, 2039 (1950).
[5] K. Takeshita, *J. Chem. Soc. Japan* **55**, 223, 279 (1952); *Chem. Abstr.* **48**, 7545 (1954); **47**, 12228 (1953).
[6] H. Finch, K. E. Furman and S. A. Ballard, *J. Amer. Chem. Soc.* **73**, 4299 (1951).
[7] K. Takeshita, *J. Chem. Soc. Japan* **56**, 28 (1953); *Chem. Abstr.* **48**, 7545 (1954).

Under suitable conditions secondary alcohols can give products very similar to those obtained with the corresponding ketones. Thus borneol, like camphor, gives a mixture of campholic and isocampholic acid on alkali fusion.[8] Cyclohexanol can be substituted for cyclohexanone in the reactions cited above,[4] and the fission of 4-alkylcyclohexanols has been used to prepare 4-alkylhexanoic acids.[9] An unexpected variety of products has, however, been reported from the fission of 12-hydroxystearic (dihydroricinoleic) acid; in addition to dodecanedioic, heptanoic and undecanoic acids, which might be anticipated by analogy with the fission of ketones, undecanedioic, hexanoic, decanoic and stearic acid have been claimed.[10–13] The formation of hexanoic acid from 9:10:12-trihydroxystearic acid is also surprising.[14] Such reports, if valid, would indicate a novel oxidative fission. However evidence for the identity of many of the products is lacking, and some of the starting materials are known to have been impure.

To obtain further information on the behaviour of ketones and alcohols under strongly alkaline conditions, the alkali fusion of a number of keto- and hydroxy-acids has now been studied. These starting materials were chosen to ensure the introduction of the functional groups under investigation into the reaction medium, and because the products are readily analysed chromatographically.

On treatment of 12-ketostearic acid (VII, n = 5, m = 10) with molten potassium hydroxide at 300 and 360° in an inert atmosphere, the principal products, formed in approximately equimolar amounts, were heptanoic, undecanoic and dodecanedioic acid (Table 1) (traces of hexane were also detected). These may be attributed to an

$$CH_3\cdot(CH_2)_n\cdot CO\cdot(CH_2)_m\cdot CO_2H \qquad \text{VII}$$

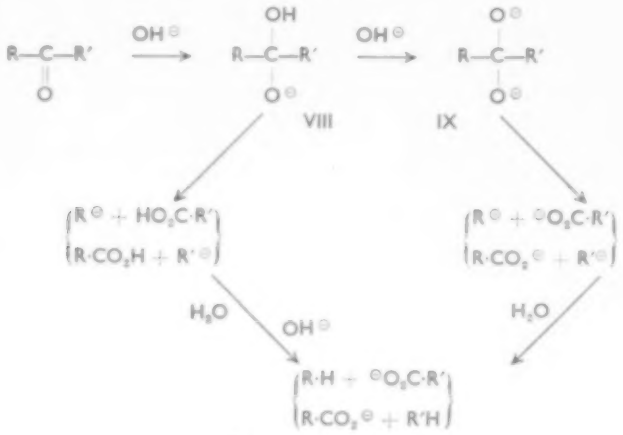
TABLE 1. ALKALI FUSION OF 12-OXO- AND HYDROXY-OCTADECANOIC ACID
(1 hr; yield of acidic products in moles)

	Keto-acid				Hydroxy-acid		
	300°	300°	360°	360°	300°	300°	300°
Mono-carboxylic acids: n-C_5	0·05	0·06	0·05	0·06	0·06	0·07	0·03
n-C_7	0·38	0·33	0·39	0·36	0·29	0·32	0·27
n-C_{11}	0·26	0·25	0·25	0·27	0·28	0·17	0·19
"10-Me-C_{10}"	*a*	*a*	0·05	0·08	*a*	*a*	*a*
High b.p. acids[b]	0·20	0·20	0·12	0·12	0·21	0·17	0·18
Di-carboxylic acids: n-C_{10}	0·07	0·06	0·10	0·10	0·05	0·09	0·08
n-$_{12}$	0·31	0·32	0·31	0·31	0·26	0·34	0·32

[a] 12-Methyloctadecenoic acids detected qualitatively.
[b] Approximate value, estimated by difference.

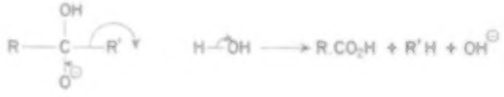
[8] M. Guerbet, *C.R. Acad. Sci., Paris* **148**, 720 (1909); *Bull. Soc. Chim. Fr.* **5**, 420 (1909).
[9] E. L. Pelton and A. A. Holzschuh, U.S. Pat. 2531363; *Chem. Abstr.* **45**, 2969 (1951).
[10] L. A. Mikeska, U.S. Pat. 2614122; *Chem. Abstr.* **47**, 5431 (1953).
[11] M. Kobayashi, *J. Oil Chem. Soc. Japan* **2**, 183 (1953); *Chem. Abstr.* **48**, 9718 (1954).
[12] R. L. Logan, U.S. Pat. 2777865; *Chem. Abstr.* **51**, 14296 (1957).
[13] T. R. Steadman and J. O. H. Peterson, *Industr. Engng. Chem.* **50**, 59 (1958).
[14] R. L. Logan, U.S. Pat. 2625558; *Chem. Abstr.* **47**, 10551 (1953).

initial attack of the carbonyl group by hydroxyl ion to give either VIII or IX, followed by equal fission of the 11:12 and 12:13 bonds (Scheme 1).



Scheme 1

It seems unlikely that the carbanions indicated in the above scheme have a free existence;[15] they are probably transferred directly to an acceptor such as water (e.g. Scheme 2).



Scheme 2

However, the yield of undecanoic acid was always lower than that of heptanoic and dodecanedioic acid, and no large amount of hexane was ever obtained. An alternative acceptor, presumably the ketone itself,[5] must therefore play a rôle (e.g. Scheme 3).

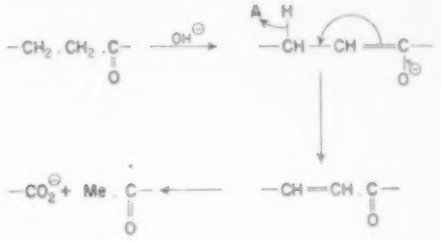
Scheme 3

Partial dehydration of tertiary alcohols formed in this way, followed by isomerization of the resulting olefins and fission reactions of the Varrentrapp type, would then account for the complex mixture of high boiling acids observed in the products. [The transformations, referred to above, leading to V and VI may also be simply explained along similar lines.] Evidence for side reactions of these types was provided by studies on 10-keto-stearic acid (see below).

Two minor by-products from the alkali fusion of 12-keto-stearic acid were valeric and sebacic acid. These cannot be attributed to further reaction of heptanoic and

[15] H. M. Walborsky and F. J. Impastato, *Chem. & Ind.* 1690 (1958).

dodecanedioic acid (cf. conversion of decanoic into octanoic acid, Part I), since no degradation of the undecanoic acid to nonanoic acid was detected. It is conceivable that an initial dehydrogenation of the ketone, similar to, but occurring more rapidly than, that postulated for acids led to a mixture of $\alpha\beta$-unsaturated ketones which then underwent fission to give the observed by-products (Scheme 4). The detection of



Scheme 4

traces of a simple ketone (semicarbazone), which did not separate from an authentic specimen of octan-2-one in a mixed gas-liquid chromatogram, lends support to this view. (The reported formation of palmitic acid from stearone[7] may have been due, at least partially, to a similar process.) Another by-product observed was formulated as 10-methylpalmitic acid from the chromatographic behaviour of its methyl ester, and by analogy with products from 10-oxo-octadecanoic and 5-oxoheptadecanoic acids.

Alkali fusion of 10-ketostearic acid (VII, n = 7, m = 8) gave results very similar to those obtained with the 12-keto-isomer. In addition to the expected acids (Table 2),

TABLE 2. ALKALI FUSION OF 10-OXO- AND HYDROXY-OCTADECANOIC ACID
(1 hr; yield of acidic products in moles)

	Keto-acid				Hydroxy-acid	
	300°	300°	360°	360°[a]	300°	360°
Mono-carboxylic acids: n-C_7	0·07	0·11	0·05	0·11	0·07	0·06
Mono-carboxylic acids: n-C_9	0·42	0·30	0·42	0·42	0·41	0·34
Mono-carboxylic acids: "8-Me-C_{10}"	0·02	0·02	0·07	0·07	0·01	0·01
Mono-carboxylic acids: "10-Me-oleics"	0·04	0·05	—	—	0·05	—
High b.p. acids[b]	0·24	0·30	0·12	0·22	0·13	0·22
Di-carboxylic acids: n-C_8	0·04	0·07	0·07	0·10	0·05	0·04
Di-carboxylic acids: n-C_{10}	0·30	0·33	0·31	0·29	0·31	0·23

[a] Using 20 parts by weight of potassium hydroxide instead of 3.
[b] Approximate value, estimated by difference.

octane was also isolated in low yield and identified by a mixed gas-liquid chromatogram with an authentic specimen. The fortuitous circumstance that fission of the 9:10 bond can give 2 moles of nonanoic acid accounts for the high yield of the latter

compared with sebacic acid. That there is no selective fission of the 9:10 bond in a 10-keto-acid was confirmed with 10-oxoheptadecanoic acid (III, n = 6, m = 8). This gave octanoic and sebacic acids in equal amounts; the yield of nonanoic acid formed simultaneously was, as expected, lower (Table 3).

TABLE 3. ALKALI FUSION OF 10-OXOHEPTADECANOIC ACID
(1 hr; yield of main acidic products in moles)

		300°	300°	300°[a]
Mono-carboxylic acids	n-C_6	0·06	0·09	0·08
	n-C_7	0·01	—	0·02
	n-C_8	0·26	0·30	0·29
	n-C_9	0·16	0·13	0·18
	"10-Me—C_{17} (unsatd.)"	0·06	0·05	0·06
High b.p. acids[b]		0·35	0·32	0·21
Di-carboxylic acids	n-C_8	0·03	0·05	0·05
	n-C_{10}	0·26	0·30	0·25

[a] Using 20 parts by weight of potassium hydroxide instead of 3.
[b] Approximate value, estimated by difference.

Chromatography of the methyl esters of the product obtained on alkali fusion of 10-ketostearic acid at 300° gave a band with a retention volume slightly greater than that of methyl palmitate, and two others both with retention volumes slightly greater than that of methyl oleate. Similar examination of the product from a reaction at 360° indicated that the acids responsible for the last two bands had been converted, under the more drastic conditions, into that giving rise to the first. Ozonolysis of the lower temperature product destroyed the acids similar to oleic and gave a mixture which was shown chromatographically to contain decan-2-one (semicarbazone), octanoic acid, azelaic acid and (probably) 10-oxoundecanoic acid. The unsaturated acids are therefore regarded as 10-methyloctadecenoic acids (mainly Δ^9 and Δ^{10} isomers), and the acid similar to palmitic as 8-methylpalmitic acid arising from further reactions of the Varrentrapp type. The initial production of the methyloctadecenoic acids may be attributed to the following sequence of reactions: (i) formation of decan-2-one and 10-oxoundecanoic acid as in Scheme 4, (ii) conversion of these ketones into 10-hydroxy-10-methyloctadecanoic acid by reactions similar to those in Scheme 3, and (iii) dehydration. Ozonolysis also gave di-n-octyl ketone and 10-ketostearic acid. These latter degradation products, together with octanoic and azelaic acid already mentioned, indicate the formation (during alkali fusion) of branched chain olefins by reactions similar to those just discussed, but in which the original keto-acid serves as both donor and acceptor of carbanions (Scheme 3).

As expected by analogy with 10-keto-stearic acid, alkali fusion (300°/1 hr) of the symmetrical nonadeca-10-onedioic acid X gave mainly sebacic (0·60–0·76 mole) and nonanoic acid (0·42–0·57 mole)

$$HO_2C{\cdot}(CH_2)_8{\cdot}CO{\cdot}(CH_2)_8{\cdot}CO_2H \qquad X$$

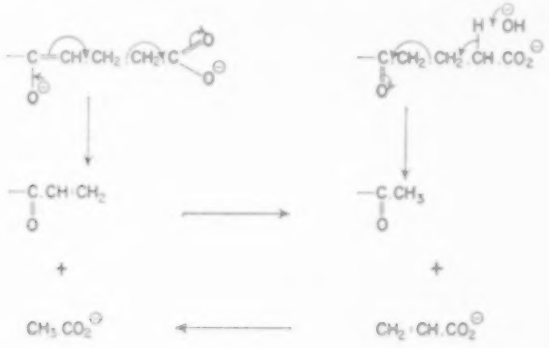
The alkali fusion of 5-oxoheptadecanoic acid (VII, n = 11, m = 3) proved somewhat anomalous (Table 4). Though tridecanoic acid was formed in good yield, only

TABLE 4. ALKALI FUSION OF 5-OXOHEPTADECANOIC ACID
(1 hr; yield of acidic products in moles)

	300°	300°	300°[a]	300°	300°
C_2[b]				0·26	0·40
n-C_4				0·07	0·10
n-C_{11}	0·04	0·02	0·02	0·02	0·02
n-C_{13}	0·20	0·25	0·34	0·23	0·26
n-C_{15}	0·05	0·08	0·04	0·03	0·03
"3-Me—C_{15}"	0·06	0·15	0·07	0·07	0·07
High b.p. acids[c]	0·23	0·28	0·16	0·28	0·22

[a] Using 20 parts by weight of potassium hydroxide instead of 3.
[b] *p*-Bromophenacyl ester, m.p. and mixed m.p. 83°.
[c] Approximate value, estimated by difference.

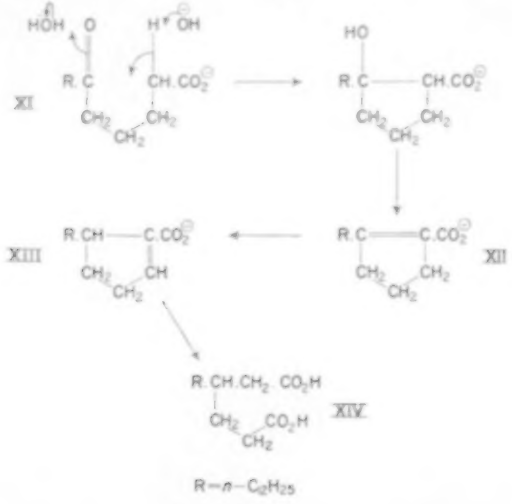
small amounts of butyric and glutaric were obtained. This suppression of the usual reactions suggests that fission of a 5-keto-acid occurs mainly by alternative routes involving reactions of the "retro-Michael" type (Scheme 5).



Scheme 5

The resulting methyl ketone may then undergo "normal fission", or attack by a carbanion leading eventually to a 3-methyl acid and other products. It is consistent with this interpretation that 5-oxoheptadecanoic acid gave unusually high yields of acetic acid (25–40 per cent; cf. 10 per cent from 10-ketostearic acid) and an acid, the methyl ester of which did not separate from an authentic specimen of methyl 3-methylpentadecanoate in a mixed chromatogram. Another by-product detected was tentatively identified as pentadecanoic acid from the retention volume of its methyl ester and its resistance to ozonolysis. Its formation may be attributed to reduction of the keto-acid to the corresponding hydroxy acid, by aldehydes formed in the fission of $\alpha\beta$-unsaturated ketone and acid intermediates (cf. the reduction of ketones by primary alcohols discussed below), followed by dehydration and a Varrentrapp fission of the resulting unsaturated acid. The formation of pentadecanoic acid can thus be regarded as a further consequence of the greater importance with 5-keto-acids of reactions giving aldehydes or other hydride ion donors.

Further departures from the general pattern of ketone fission must be expected with appropriately substituted compounds. Alkali fusion of 6-ketostearic acid XI gave only small amounts of tridecanoic and adipic acid, by fission of the 5:6 and 6:7 bonds respectively (Scheme 1). The main products isolated were an $\alpha\beta$-unsaturated acid, which was shown to be the cyclopentenyl derivative XII by ozonolysis to 5-ketoheptadecanoic acid, and a saturated C_{18}-dicarboxylic acid, which was shown to be β-dodecyladipic acid XIV by comparison with a sample synthesised unambiguously. On further reaction with molten alkali XII was converted into XIV in 50 per cent yield. The initial production of the cyclopentenyl acid may be attributed (Scheme 6) to our intramolecular reaction of the aldol or Claisen type, followed by dehydration of the resulting β-hydroxy-acid (cf. conversion of 2-hydroxycyclohexanecarboxylic acid into cyclohexenecarboxylic acid[16]). The isolation of an $\alpha\beta$-unsaturated acid from an alkali fusion was unexpected, but is no doubt associated with the fact that direct fission of XII merely regenerates 6-ketostearic acid. Isomerization of XII to XIII, by a prototropic migration of the double bond, followed by a fission of the Varrentrapp type, accounts satisfactorily for the formation of XIV (cf. isomerization and fission of octadec-2-enoic acid, Part I, and the conversion of cyclohexenecarboxylic acid into pimelic acid[16]).



Scheme 6

On prolonged reaction in molten alkali, XIV was converted into a mixture of acids, probably branched chain C_{17}-acids.

Attention was next directed to the reaction of hydroxy-acids. Alkali fusion of 12-hydroxystearic acid (XV, n = 5, m = 10) gave, in very similar yields, the same products as 12-ketostearic acid (Table 1). Undecanedioic acid, reported by some previous authors as the principal product,[12,13] was not detected, nor were hexanoic, decanoic or stearic acid (cf. 10–13). However, when the reaction was carried out in

$$CH_3{\cdot}(CH_2)_n{\cdot}CHOH{\cdot}(CH_2)_m{\cdot}CO_2H \qquad XV$$

[16] H. J. Pistor and H. Plieninger, *Liebigs Ann.* **562**, 239 (1949); F. X. Werber, J. E. Jansen and T. L. Gresham, *J. Amer. Chem. Soc.* **74**, 532 (1952).

an atmosphere of oxygen, all n-monocarboxylic acids from C_5 to C_{11} and all n-dicarboxylic acids from C_8 to C_{12} were detected in small amounts. Oxygenation of the intermediate carbanions, and subsequent dehydrogenation (see below), probably accounts for the production of the lower homologues of the main products obtained from fusions in an inert atmosphere. Such side reactions cannot predominate over the reactions discussed previously for the formation of acids, and cannot therefore be invoked to justify the anomalous reports to which reference has already been made.

Scheme 7

The products from the alkali fusion of 10-hydroxystearic acid (XV, n = 7, m = 8) were also the same as those from the corresponding keto-acid (Table 2), and alkali fusion of 6-hydroxystearic acid, (XV, n = 11, m = 4) gave both XII and XIV. This close similarity between the products from the hydroxy- and keto-acids, particularly in the 6-oxygenated series, implied that reaction of the hydroxy compounds involved an initial dehydrogenation to give the corresponding ketones. The formation of camphor during the fission of borneol with molten alkali was reported by Guerbet,[8] but the significance of this observation does not seem to have been appreciated. A recent study of the alkaline fission of 12-hydroxy- and 12-keto-stearic acid afforded no evidence of such a conversion.[13] However, it has now been shown that treatment of 12- and 10-hydroxystearic acid with either molten alkali at 200–260°, or with 30 per cent aqueous potassium hydroxide at 300° gives the corresponding keto-acids and hydrogen (Table 5). These reactions occur in both metal and glass vessels; the

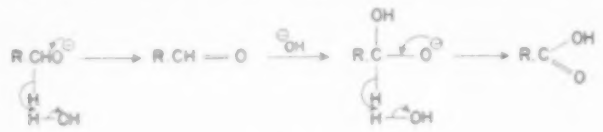
Table 5. Dehydrogenation of 10- and 12-hydroxy-octadecanoic acid

Apparatus		Alkali[a]	Temp.	Time	Yield of ketone (%)	
					Spectral[b]	Isolated
12-Hydroxy-acid	glass	KOH–NaOH	200–210°	1 hr	41	—
	glass	KOH–NaOH–CdO	200–210°	1 hr	66	—
	copper	KOH–NaOH	200–210°	1 hr	36	—
	nickel	KOH–NaOH	200–210°	1 hr	25	—
	nickel	KOH–NaOH–CdO	200–210°	1 hr	60	35
	nickel	KOH–NaOH	250–260°	1 hr	45	30[d]
	steel[c]	30% KOH	360°	2 hr	80	60
	steel[c]	30% KOH–CdO	300°	2 hr	90	76
	steel[c]	60% KOH–CdO	300°	1 hr	71	45
10-Hydroxy-acid	nickel	KOH–NaOH	240–250°	1 hr	45	30[d]
	nickel	KOH–NaOH–CdO	250–260°	1 hr	41	30[d]

[a] KOH–NaOH represents a 1 : 1 mixture of the two alkalis which form a low melting eutectic; cadmium oxide (ca. 10% by weight of the acid used) was added where indicated.
[b] Estimated from the intensity of the carbonyl absorption at 1715 cm^{-1} after esterification of the product.
[c] Autoclave.
[d] Products formed by fission of the ketone were also detected.

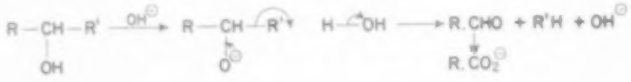
addition of cadmium oxide (claimed to promote the dehydrogenation of primary alcohols and the fission of ricinoleic and dihydroricinoleic acid[13,17]) seemed to favour keto-acid formation, but the number of experiments performed do not warrant a generalisation at this stage.

The dehydrogenation of secondary alcohols to ketones is depicted in Scheme 7. The well known dehydrogenation of primary alcohols to carboxylates on alkali fusion, first observed by Dumas and Stass,[18] may be represented similarly (Scheme 8).



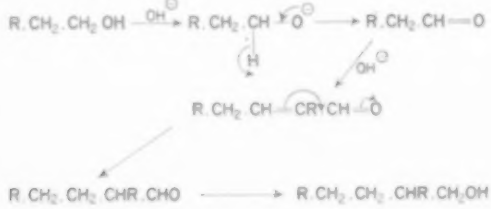
Scheme 8

Though reactions of secondary alcohols in strong alkalis have now been shown to involve dehydrogenation to the corresponding ketones, the possibility cannot be excluded of simultaneous fission by a mechanism of the type shown in Scheme 9. With β-hydroxy-acids such a pathway even seems to be preferred (Part I).



Scheme 9

Though not examined in the present studies, reference must also be made to another reaction of alcohols under strongly alkaline conditions. Guerbet demonstrated that both primary and secondary alcohols, when heated with their alkali metal alcoholates under essentially anhydrous conditions, yield "dimeric" alcohols and higher condensation products.[19] These reactions may be regarded as involving an aldol condensation, and hydride ion transfers from either the alcoholate, or a derived aldehyde, to the



Scheme 10

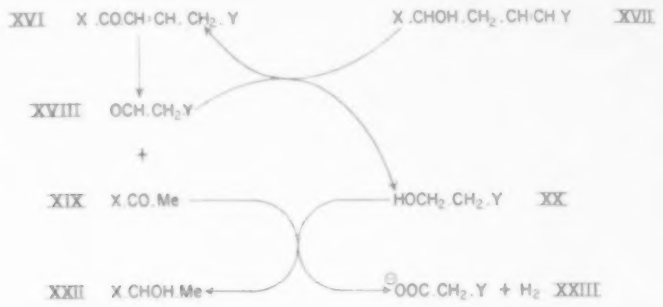
[17] H. P. Chitwood, U.S. Pat. 2384817; *Chem. Abstr.* **40**, 354 (1946); Brit. Pat. 601, 817; *Chem. Abstr.* **42**, 7325 (1948); W. Stein, Brit. Pat. 698154; *Chem. Abstr.* **48**, 6147 (1954); U.S. Pat. 2696501; *Chem. Abstr.* **49**, 2760 (1955).

[18] J. Dumas and J. S. Stass, *Liebigs Ann.* **35**, 129 (1840); cf. M. Guerbet, *Bull. Soc. Chim. Fr.* **11**, 164 (1912); E. E. Reid, H. Worthington and A. W. Larchar, *J. Amer. Chem. Soc.* **61**, 99 (1939).

[19] M. Guerbet, *Ann. Chim. Phys.* **27**, 67 (1902); *Bull. Soc. Chim. Fr.* **11**, 279 (1912); cf. C. Weizmann and S. F. Garrard, *J. Chem. Soc.* **117**, 324 (1920); C. Weizmann, M. Sulzbacher and E. Bergmann, *Ibid.* 772 (1947); W. Markownikow and P. Zubow, *Ber. Dtsch. Chem. Ges.* **34**, 3246 (1901); J. Bolle and L. Bourgeois, *Mém. Serv. Chim. État* **41**, 87 (1957); E. G. E. Hawkins and W. E. Nelson, *J. Chem. Soc.* 4704 (1954).

$\alpha\beta$-unsaturated carbonyl compound and its dihydroderivative (e.g. Scheme 10; cf.[20-22]). With primary alcohols the Guerbet reaction is frequently accompanied, or followed, by a dehydrogenation of the Dumas–Stass type.[19,23]

The results presented above throw new light on the course of the industrially important fission of ricinoleic acid (XVII) in concentrated alkalis.[24,25] It is well known that octan-2-one (XIX) and 10-hydroxydecanoic acid (XX) are the principal products formed at ca. 200°, but that mainly octan-2-ol (XXII) sebacic acid (XXIII) and hydrogen are obtained at temperatures above 240° (Scheme 11). The formation of the low temperature products is understandable if it is assumed that ricinoleic acid, like 12-hydroxystearic acid, first undergoes dehydrogenation. Isomerization of the resulting $\beta\gamma$-unsaturated ketone into the $\alpha\beta$-isomer (XVI), followed by a fission



$$\left[X = CH_3.(CH_2)_5. \ , \ Y = (CH_2)_7.CO_2^{\ominus}\right]$$

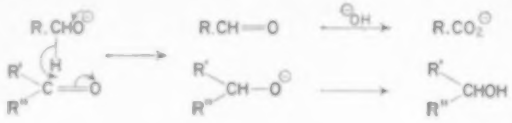
Scheme 11

of the "retro-aldol" type, would then give octan-2-one (XIX) and the aldehydo-acid (XVIII) (cf.[26]). The isolation of the hydroxy-acid (XX) rather than XVIII may be attributed to the latter's acting as a hydride ion acceptor in the initial dehydrogenation (cf. Cannizzaro and Guerbet reactions in which hydride ions are also transferred to aldehydes). Preliminary experiments indicate that addition of the aldehydo-acid[25] (XVIII) to the reaction mixture enables the fission of ricinoleic acid to be carried out at temperatures ca. 20–30° lower than those required in the absence of this or another initiator, and that the formation of octan-2-ol is appreciably reduced in such "promoted" reactions.

Hargreaves and Owen[25] have demonstrated that the products from the high temperature fission of ricinoleic acid are formed by further interaction of the low temperature products, and have cited many other examples of the reduction of ketones to secondary alcohols by treatment with primary alcohols and alkali. Such

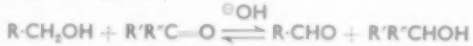
[20] W. Hückel and H. Naab, *Ber. Dtsch. Chem. Ges.* **64**, 2137 (1931).
[21] C. Weizmann, E. Bergmann and L. Haskelberg, *Chem. Industr.* **56**, 589 (1937); C. Weizmann, E. Bergmann and M. Sulzbacher, *J. Org. Chem.* **15**, 54 (1950).
[22] A. Lüttringhaus, *Angew. Chem.* **62**, 87 (1950); **63**, 244 (1951).
[23] B. W. Howk, U.S. Pat. 2293649; *Chem. Abstr.* **37**, 978 (1943).
[24] M. J. Bouis, *C.R. Acad. Sci., Paris* **33**, 141 (1851); **41**, 603 (1859).
[25] G. H. Hargreaves and L. N. Owen, *J. Chem. Soc.* 753 (1947).
[26] G. W. Ellis, *J. Chem. Soc.* 9 (1950).

hydrogen transfers indicate that ketones can compete efficiently with water as hydride ion acceptors from the intermediates involved in the Dumas–Stass dehydrogenation of primary alcohols to carboxylates (e.g. Scheme 12). The products of both low and high temperature fission of ricinoleic acid can therefore be readily explained in terms of the present concepts.



Scheme 12

One feature of the above proposals deserves further comment. It will be noted that the low temperature products are regarded as being formed by conversion of a secondary alcohol and an aldehyde into a ketone and a primary alcohol respectively, and the high temperature products by a subsequent reduction of a ketone by a primary alcohol. This apparent contradiction is resolved by the reasonable assumption that a hydrogen transfer of the type shown in Scheme 13 is reversible (cf. Meerwein–Ponndorf and Oppenauer reactions):

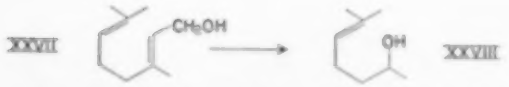


Scheme 13

In most examples, equilibrium is disturbed by the (non-reversible) conversion of aldehyde into carboxylate, and the formation of secondary alcohol is therefore favoured. In the initial stage of the ricinoleic acid reaction, however, the ketone formed is unsaturated and hence destroyed by fission; the reaction therefore proceeds in the reverse direction with reduction of the aldehyde. The ability of secondary alcohols to reduce aldehydes under appropriate alkaline conditions is also implicit in the observation of Doering and Aschner[27] that (−)-active amyl alcohol is racemized in the presence of both alkalis and ketones, but not of alkalis alone. This result is attributed to dehydrogenation, and reformation, of the primary alcohol by reactions of the type generalized in Scheme 13, and racemization of the intermediate aldehyde.[27]

The mechanisms proposed in this paper can obviously be extended to embrace the fission not only of other $\beta\gamma$-unsaturated alcohols, e.g. of isopulegol (XXIV) to

XXVI $HOCH_2.CH_2.CH{:}CH.(CH_2)_2.CH_2OH \rightarrow HO_2C.CH_3 + HO_2C.(CH_2)_3.CO_2H$



[27] W. von E. Doering and T. C. Aschner, *J. Amer. Chem. Soc.* **71**, 839 (1949); **75**, 393 (1953).

3-methylcyclohexanol (XXV),[28] and of hept-3-ene-1:7-diol (XXVI) to glutaric and acetic acids,[29] but also of allylic alcohols,[30] e.g. of geraniol (XXVII) to methylheptenol (XXVIII).[31]

The behaviour of systems with two vicinal oxygen functions will be considered in Part IV.

EXPERIMENTAL

The general procedures and analytical methods used were those described in Part I, except that both mono- and dicarboxylic acids were analysed by gas-liquid chromatography (G.L.C.) of their methyl esters. The sources of starting materials not mentioned in Part I are indicated below:

Keto-acids. 6- and 10-Oxo-octadecanoic acid were prepared by the method of Bergstrom *et al.*[32] 5- and 10-Oxoheptadecanoic acid were prepared similarly (ca. 60%) and had m.p. 84·5–86° (Found: C, 71·8; H, 11·3. $C_{17}H_{32}O_3$ requires: C, 71·8; H, 11·35%), and 77·8–78·5° respectively (Found: C, 71·95; H, 11·15%). 12-Oxo-octadecanoic acid was prepared by oxidation of methyl 12-hydroxyoctadecanoate in benzene with chromic acid in aqueous acetic acid (cf.[33]), and hydrolysis of the product; the keto-acid had m.p. 80·0–81·4° (lit.[32] m.p. 81·5–82°). Nonadec-10-onedioic acid was prepared by the method of Blomquist *et al.*[34]

Hydroxy-acids. Potassium borohydride (5·0 g) in 2% KOH (50 cc) was added over 30 min to a stirred solution of 10-oxo-octadecanoic acid (15 g) in 10% KOH (150 cc) at 100°. The mixture was stirred at 100° for a further 2 hr. Isolation of the product, and crystallization from methanol, gave 10-hydroxyoctadecanoic acid (12 g), m.p. 79–80° (lit.[32] m.p. 79·2–79·5°); the infra-red spectrum of the methyl ester showed no ketone absorption. 6-Hydroxyoctadecanoic acid was prepared similarly in 70% yield and had m.p. 81·8–82·6° (lit.[32] m.p. 82·0–82·4°).

Ricinoleic acid was prepared from castor oil (B.P. grade), via the barium salt (cf.[35]), and had m.p. 2–3°, n_D^{24} 1·4735 (Found: I.V. 84. Calc: I.V. 85·5). Esterification (MeOH–HCl) gave the methyl ester, b.p. 188–190°/2 mm, n_D^{20} 1·4633 (lit.[36] b.p. 185°/2 mm, n_D^{20} 1·4628); ν_{max} 3460 (—OH) and 1736 cm^{-1} (—CO_2Me), bands due to conjugated dienes were absent. Catalytic reduction of methyl ricinoleate (50 g) in methanol (200 cc) over W-6 Raney nickel at 160°/150 atm, and crystallization from the same solvent, gave methyl 12-hydroxyoctadecanoate (37·5 g), m.p. 56–57° (lit.[37] m.p. 57–58° for the optically active form). Hydrolysis with hot 10% KOH, and crystallization from alcohol, gave (84%) 12-hydroxyoctadecanoic acid, m.p. 80–81·5° (lit.[37] m.p. 80·5–81° for the optically active form).

Alkali fusions. Unless otherwise stated, these were performed as described in Part I. The temperatures quoted are bath temperatures. The reaction products were cooled and dissolved in water. The clear solutions were acidified with hydrochloric acid, and the resulting mixtures extracted with light petroleum (b.p. 40–60°). Any insoluble acids (mainly dicarboxylic) were filtered off and washed with light petroleum. The petroleum solutions were combined, washed with water, dried (Na_2SO_4) and evaporated at ca. 40° under reduced pressure until the weights of the residues (mainly monocarboxylic acids) were constant. The aqueous solutions were extracted with ether, evaporated to dryness, and the residues extracted thoroughly with ether (Soxhlet). The ethereal solutions were combined with the petroleum insoluble acids and evaporated until the weights of the residues (mainly di-carboxylic acids) were constant. The products were either analysed by G.L.C. of their methyl esters (see Tables), or purified as indicated in the examples given below:

[28] *Ber. Schimmel*, p. 91. Oct. (1913).
[29] F. Runge, R. Hueter and H. -D. Wulf, *Chem. Ber.* **87**, 1430 (1954).
[30] G. H. Hargreaves and L. N. Owen, *J. Chem. Soc.* 756 (1947).
[31] P. Barbier, *C.R. Acad. Sci., Paris* **126**, 1423 (1898); F. Tiemann, *Ber. Dtsch. Chem. Ges.* **31**, 2989 (1898); J. Doeuvre, *Bull. Soc. Chim. Fr.* **45**, 351 (1929).
[32] S. Bergstrom, G. Aulin-Erdtman, B. Rolander, E. Stenhagen and S. Ostling, *Acta Chem. Scand.* **6**, 1157 (1952); cf. J. Cason, *Chem. Rev.* **40**, 15 (1947).
[33] O. Grummitt and K. G. Siedschlag, *J. Amer. Oil Chem. Soc.* **26**, 690 (1949).
[34] A. T. Blomquist, J. R. Johnson, L. I. Duiguid, J. K. Shillington and R. D. Spenser, *J. Amer. Chem. Soc.* **74**, 4203 (1952).
[35] I. V. Gulbenkian and J. H. Skellon, *J. Appl. Chem.* **9**, 224 (1959).
[36] J. B. Brown and N. D. Green, *J. Amer. Chem. Soc.* **62**, 738 (1940).
[37] F. Strauss, H. Heinze and L. Salzmann, *Ber. Dtsch. Chem. Ges.* **66B**, 631 (1933).

Fission of 12-*hydroxyoctadecanoic acid*

The hydroxy acid (2·67 g) and KOH (8 g) were heated at 300° for 1 hr, and the crude products isolated by the standard procedure. Crystallization of the dicarboxylic acid fraction (0·92 g) from water gave dodecanedioic acid, m.p. and mixed m.p. 127–128° (lit.[38] m.p. 127·5–128·5°). Distillation of the esters of the mono-carboxylic acid fraction, gave (i) impure methyl heptanoate and (ii) methyl undecanoate which was converted into N-benzyl undecanoamide, m.p. and mixed m.p. 78–79°.

Fission of 10-*oxo-octadecanoic acid*

The keto-acid (5 g) and KOH (15 g) were heated (in two batches) at 300–320° for 1 hr, and the product was cooled and dissolved in water (200 cc). The solution was acidified with 2 N HCl, and then steam distilled until a clear distillate was obtained. The distillate (500 cc) was neutralized with 2 N NaOH and concentrated. The residue (ca. 50 cc) was acidified and then extracted with ether. The ethereal solution was washed, dried (Na_2SO_4) and evaporated giving nonanoic acid (1·23 g) (*p*-bromophenacyl ester, m.p. and mixed m.p. 68–69°), which was shown to contain 8% of heptanoic acid by G.L.C. of the methyl esters.

The residue from the steam distillation was extracted (2 × 100 cc) with light petroleum (b.p. 40–60°). The extract was filtered and the insoluble solid dissolved in ether. The aqueous mother liquors were extracted (2 × 50 cc) with ether and all the ethereal solutions were combined, washed with water, dried (Na_2SO_4) and evaporated. The residue (1·42 g) was shown to contain 85% sebacic acid and 15% suberic acid by G.L.C. of the methyl esters. Crystallization of a portion (1·0 g) from water gave sebacic acid (0·53 g), m.p. and mixed m.p. 134°.

The light petroleum solution was dried and evaporated giving a mixture of acids (1·80 g) which was shown by G.L.C. of the methyl esters to contain 6% of nonanoic acid, 2% of 8-methylhexadecanoic acid, and 11% of 10-methyloctadecenoic acids (octanoic, azelaic and 10-oxo-octadecanoic acids were absent). A portion of the mixture (0·9 g) was ozonized in acetic acid–methyl acetate by the procedure described in Part I. After decomposition of the ozonide with hydrogen peroxide, the mixture was neutralized with aqueous potassium hydroxide. The neutral products were isolated with ether and steam distilled; extraction of the distillate with ether gave decan-2-one (G.L.C. and mixed G.L.C. with an authentic specimen), semicarbazone, m.p. and mixed m.p. 123–124° (lit [39] m.p. 125–126°). Extraction of the residues from the steam distillation with ether gave di-*n*-octyl ketone (G.L.C. and mixed G.L.C. with an authentic specimen), m.p. 46–48° undepressed on admixture with an authentic specimen, m.p. 49–50° (lit.[40] m.p. 50°).

After removal of the neutral products of ozonolysis, the alkaline solution was acidified and the acidic products extracted (2 × 100 cc) with light petroleum (b.p. 40–60°). The extract was washed with water, dried and evaporated giving a solid (0·42 g), which was esterified ($MeOH–H_2SO_4$). Analysis of the methyl esters by G.L.C. revealed 4% of methyl heptanoate, 20% of methyl octanoate, 13% methyl nonanoate, and 15% of an ester, probably methyl 10-oxoundecanoate. Crystallization of the methyl esters from aqueous methanol (charcoal) gave methyl 10-oxo-octadecanoate (0·1 g) as plates, m.p. and mixed m.p. 45–46° (lit.[22] m.p. 45·8–46·1°); ν_{max} 1733 (—CO_2Me) and 1706 cm^{-1} (—CO—).

The aqueous mother liquors from the petroleum extraction were steam distilled (to remove acetic acid) and then extracted (2 × 100 cc) with ether. The extract was washed, dried and evaporated. The residue (0·3 g) was esterified ($MeOH–H_2SO_4$) and the resulting methyl esters were shown by G.L.C. to contain 2% of methyl pimelate, 8% of methyl suberate and 46% of methyl azelate; a band (ca. 15%), which did not separate from either methyl 10-oxoundecanoate or methyl sebacate, was also observed before, but not after, treatment of the mixture with Girard reagent P.

Alkali fusion of 6-*oxo-octadecanoic acid*

(*i*) The keto-acid (5·2 g) and KOH (9 g) were heated at 280–300° for 2 hr and the products isolated by the standard procedure. A solution of the mono-carboxylic acid fraction (3·2 g) in light petroleum (b.p. 40–60°) (40 cc) was decolourized with charcoal and then cooled to 0°. The solid (1·6 g), m.p.

[38] B. W. Baker, R. W. Kierstead, R. P. Linstead and B. C. L. Weedon, *J. Chem. Soc.* 1804 (1954).
[39] T. Shenton and J. C. Smith, *Chem. & Ind.* 1510 (1958).
[40] F. L. Breusch and F. Baykut, *Chem. Ber.* **86**, 684 (1953).

77–78°, which separated was collected and crystallized from aqueous alcohol to give *2-dodecylcyclopent-1-ene carboxylic acid* (1·0 g) as plates, m.p. 82–83° (Found: C, 76·8; H, 11·65. $C_{19}H_{32}O_2$ requires: C, 77·1; H, 11·5%); λ_{max} 233 mμ, ε = 11,800; ν_{max} 1667 (conjug. CO_2H) and 1623 cm^{-1} (conjug. C=C). On hydrogenation in acetic acid over Adams catalyst, the cyclopentenyl acid absorbed 0·92 mole of hydrogen; the product had m.p. 50·6–51·3° (Found: C, 76·7; H, 12·35. $C_{19}H_{34}O_2$ requires: C, 76·55; H, 12·15%). The cyclopentenyl acid (0·42 g) was ozonized by the procedure described in Part I. The water insoluble product was separated and extracted with light petroleum (b.p. 40–60°). The insoluble residue (0·25 g) was crystallized from aqueous methanol and gave 5-oxoheptadecanoic acid, m.p. 86·5–87·0° (Found: C, 71·75; H, 11·35; O, 16·65%; equiv., 273. Calc. for $C_{17}H_{32}O_3$: C, 71·8; H, 11·35; O, 16·9%; equiv., 284), which did not depress the m.p. of an authentic specimen.

(ii) The keto-acid (3·0 g) and KOH (9 g) were heated at 300–320° for 1 hr and the products isolated as usual. Crystallization of the petroleum insoluble acids (1·17 g) from aqueous alcohol gave *β-dodecyladipic acid* (0·7 g) as needles, m.p. 85–86° (Found: C, 68·85; H, 11·1%; equiv. 156; mol. wt. 337. $C_{18}H_{34}O_4$ requires C, 68·75; H, 10·9%; equiv. 157; mol. wt. 315). The m.p. was undepressed on admixture with an authentic specimen (see below), which had an identical infra-red light absorption spectrum. The m.p. was depressed on admixture with the starting material.

Tridecanoic acid was detected in the petroleum soluble fraction by G.L.C. of the methyl esters. Evaporation of the aqueous mother liquors from the reaction product, and extraction with ether gave traces of adipic acid (identified by paper chromatography).

Alkali fusion of 6-hydroxyoctadecanoic acid

(i) The hydroxy-acid (3·0 g) and a finely powdered mixture (1 : 1, 9 g) of sodium and potassium hydroxides were heated at 250–260° for 1 hr. Isolation of the products in the usual way gave a petroleum soluble fraction (2·4 g). Crystallization from light petroleum (b.p. 40–60°) and then from methanol (charcoal) gave 2-dodecylcyclopent-1-enecarboxylic acid (1·2 g, 50%), m.p. and mixed m.p. 82–83°.

(ii) The hydroxy-acid (2·2 g) and potassium hydroxide (6 g) were heated at 280–300° for 2 hr, and the products isolated in the usual way. Crystallization of the petroleum insoluble fraction from aqueous methanol gave a solid (0·5 g, 20%), m.p. 79–81°. Recrystallization from the same solvent gave β-dodecyladipic acid, m.p. and mixed m.p. 84·5–85·5°.

Fission of 2-dodecylcyclopent-1-ene carboxylic acid

The acid (1·67 g) and KOH (5 g) were heated at 300–310° for 1 hr. Isolation of the products gave (i) recovered starting material (0·36 g), m.p. and mixed m.p. 82–83°, and (ii) β-dodecyladipic acid (0·8 g), m.p. and mixed m.p. 86°.

Fission of β-dodecyladipic acid

The acid (1·7 g) and KOH (5 g) were heated at 360° for 1 hr and the products isolated in the usual way. The petroleum soluble fraction (1·3 g) was esterified (MeOH–H_2SO_4). Distillation gave an oil (1·0 g), b.p. 160–162°/3 mm, n_D^{20} 1·4433 (Found: C, 75·55; H, 12·95%; C–Me, 2·05. Calc. for $C_{15}H_{30}O_2$: C, 76·0; H, 12·75%), which probably consisted of a mixture of methyl esters of branched chain C_{17} acids; G.L.C. on Apiezon T at 240° gave two bands of comparable size and with retention volumes slightly greater than that of methyl palmitate (only one band was observed on silicone at 240°).

Alkali fusion of adipic acid under similar conditions gave valeric acid in low yield. β-Methyladipic acid gave (ca. 5–10%) an acid, the methyl ester of which did not separate from methyl 4-methylpentanoate in a mixed chromatogram on silicone.

Dehydrogenation of hydroxy-acids

(i) 12-Hydroxyoctadecanoic acid (1·00 g) and KOH (0·6 g) in water (2 cc) were heated in a nitrogen filled steel autoclave at 360° for 2 hr. The autoclave was cooled and opened, releasing a combustible gas, and the contents were dissolved in water (200 cc). The solution was acidified, and the product (0·93 g) was isolated with ether and esterified (MeOH–H_2SO_4). The intensity of the carbonyl band at 1715 cm^{-1} indicated an 80% yield of the keto-ester. Crystallization from aqueous methanol gave methyl 12-oxo-octadecanoate (0·60 g) as plates, m.p. and mixed m.p. 45–46° (lit.[32] 45·4–45·7°).

(ii) The preceding experiment was repeated, at 300° with the addition of cadmium oxide (0·1 g) to the reaction mixture, and gave methyl 12-oxo-octadecanoate (76%; spectral yield, 90%), m.p. and mixed m.p. 45–46°.

(iii) 10-Hydroxyoctadecanoic acid (1·0 g) and a finely powdered mixture (1 : 1; 3·0 g) of sodium and potassium hydroxides were heated in nitrogen in a nickel pot at 240–250° for 1 hr. Isolation of the product, esterification and crystallization from aqueous methanol gave methyl 10-oxo-octadecanoate (30%; spectral yield 45%), m.p. and mixed m.p. 45–46° (lit.[32] m.p. 45·8–46·1°).

β-Dodecyladipic acid

p-Dodecylphenol[41] (7·0 g) in alcohol (30 cc) was hydrogenated over W-6 Raney nickel at 150°/150 atmos for 6 hr. Isolation of the neutral product gave an oil (2·1 g). A portion (1·2 g) was treated with sodium dichromate (3 g) in 15% H_2SO_4 (20 cc) for 1 hr. Isolation of the product, and crystallization from methanol, gave 4-*dodecylcyclohexanone* (0·5 g), as plates, m.p. 42° (Found: C, 80·6; H, 12·95. $C_{18}H_{34}O$ requires: C, 81·15; H, 12·85%). The 2:4-*dinitrophenylhydrazone* crystallized from ethyl acetate and had m.p. 112–113° (Found: N, 12·65. $C_{24}H_{38}O_4N_4$ requires: N, 12·55%). Oxidation of the ketone (0·5 g) with conc. HNO_3 (10 cc) in the presence of ammonium vanadate (1 g) at 90° for 3 hr., isolation of the acidic product (0·4 g), and crystallization from aqueous methanol, gave β-dodecyladipic acid as plates, m.p. 86° (Found: C, 68·85; H, 11·1. Calc. for $C_{18}H_{34}O_4$: C, 68·75; H, 10·9%).

3-*Methylpentadecanoic acid*

Dodecanoic acid (15 g) and methyl hydrogen β-methylglutarate[42] (3·0 g) in methanol (100 cc) were added to sodium methoxide (from 50 mg of sodium) in methanol (200 cc), and the solution was electrolysed (2–3·5 A, 100 V) at 60° between two platinum plate electrodes (6·5 × 5 cm) until neutral (6 hr). Water (200 cc) was added and the mixture was extracted with ether. The extract was washed thoroughly with 5% KOH, dried and evaporated. The residue was treated with 10% KOH at 90° for 2 hr, and the acidic fraction isolated in the usual way. After steam distillation (to remove traces of dodecanoic acid), the crude product was esterified (MeOH–H_2SO_4). Distillation gave methyl 3-methylpentadecanoate (1·5 g), b.p. 128–130°/1 mm, n_D^{27} 1·4380 (Found: C, 75·1; H, 12·8. Calc. for $C_{17}H_{34}O_2$: C, 75·5; H, 12·65%). Hydrolysis gave 3-methylpentadecanoic acid which crystallized from acetone in plates, m.p. 36–37·5° (lit.[43] m.p. 37·2–37·7°).

Carbon and hydrogen determinations were carried out in the microanalytical laboratory (Miss J. Cuckney), and infra-red measurements in the spectroscopic laboratory (Mr. R. L. Erskine) of this Department.

Acknowledgements—One of us (R. A. D.) thanks the Department of Scientific and Industrial Research for a research studentship.

[41] N. K. Adam, W. A. Berry and H. A. Turner, *Proc. Roy. Soc.* A **117**, 539 (1927).
[42] R. P. Linstead, J. C. Lunt and B. C. L. Weedon, *J. Chem. Soc.* 3331 (1950).
[43] J. Cason, N. L. Allinger and D. E. Williams, *J. Org. Chem.* **18**, 842 (1953).

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THE STRUCTURE OF ISOPHYLLOCLADENE

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Abstract—8β-Carboxy-13-oxopodocarpane (VIa) has been prepared from isophyllocladene and its rotatory dispersion curve examined. Isophyllocladene has also been converted to 13-oxopodocarp-8(14)-ene (XIII), identical with a sample prepared from manool. Thus the structure of isophyllocladene is established as I.

THE structure I was first proposed for isophyllocladene by Brandt,[1] on the evidence of a series of oxidations and dehydrogenations. The nature of ring D was further confirmed[2] by the demonstration that the *nor*-ketone derived from phyllocladene was present in a five-membered ring and that there was only one —CH_2-grouping adjacent to the carbonyl. No evidence has been presented to confirm the gem-dimethyl grouping at C_4 or the angular methyl at C_{10}, though it seems probable that these are placed as shown. Steric factors require ring D to be attached in a *cis* manner to ring C but nothing further is proven about the stereochemistry of the molecule.

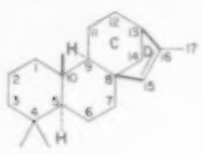
It appeared to us that the rotatory dispersion curve of the *bisnor*-keto-acid VIa (first obtained by Brandt) might cast some light on this problem and this paper describes the degradation of isophyllocladene to this compound and other products.

Treatment of isophyllocladene with osmium tetroxide gave rise to the known diol II. This was oxidized with either chromium trioxide in pyridine or 8 N chromic acid/sulphuric acid, when a mixture of products resulted. The α-ketol (VII) was formed in very small yield, the major product being an α,β-unsaturated ketone (VIII) obviously derived from the intramolecular cyclization of the keto-aldehyde (III). This had I.R. absorption in CS_2 at 1677 cm^{-1} indicative of a carbonyl group in a six-membered ring, and U.V. adsorption at 241 mμ $\varepsilon = 7800$. Wolff–Kishner reduction gave rise to a hydrocarbon most plausibly represented by IX, which, on hydrogenation, produced D-homo-dihydrophyllocladene, a new tetracyclic system.

In view of the very low yield of α-ketol (VII), splitting of the diol (II) with lead tetracetate was attempted. The resulting keto-aldehyde (III) was readily obtained; as expected, treatment with sodium hydroxide, silver oxide or even chromatography on alumina caused its cyclization to VIII. Oxidation of III with chromium trioxide in acetic acid yielded a mixture of products. The acidic fraction was treated with hydrochloric acid in methanol in order to ensure complete epimerization at C_{13}. The major product was the known keto-acid (IV), together with a small amount of the *bisnor*-keto-acid (VIa). The neutral material was separated, subjected to further oxidation and the process repeated. Finally, chromatography of the residual neutral fraction gave the epimeric keto-aldehyde (XI).

[1] C. W. Brandt, *N. Z. J. Sci. Technol.* **34B**, 46 (1952).
[2] W. Bottomley, A. R. H. Cole and D. E. White, *J. Chem. Soc.* 2624 (1955).

This structure was confirmed by warming XI with sodium hydroxide when the unsaturated ketone (VIII) was produced. It should be noted that XI could be chromatographed on alumina while its epimer (III) was partially cyclized under these conditions.



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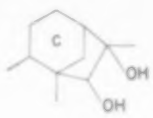

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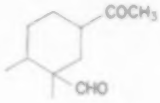

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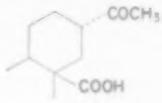

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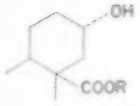
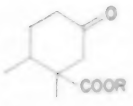
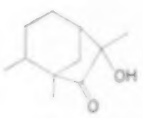


V a. R=H
b. R=Me



VI a. R=H
b. R=Me



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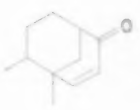
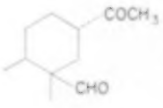


VIII

IX

X



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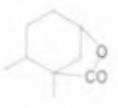

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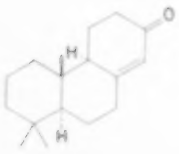
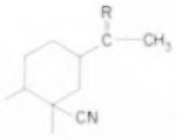
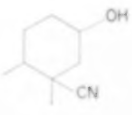


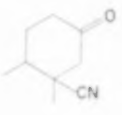
XIII



XIV a. R=NOAc
b. R=NOH
c. R=O



XV



XVI

When the keto-acid (IV), the major product of the previous oxidation, was further oxidized with pertrifluoroacetic acid and the product hydrolysed, the trans-hydroxy acid (Va) was formed. This was readily oxidized to the required *bisnor*-keto-acid (VIa). The methyl ester (Vb) was not obtained crystalline, but a qualitative comparison of its rate of hydrolysis with that of VIb, confirmed the placing of the carbonyl group γ- to the carboxyl.[3]

The rotatory dispersion curve of VIb was determined and found to be identical with that of the keto-acid prepared independently by Briggs *et. al.*[4] A full discussion of the stereochemical possibilities for phyllocladene, based on the positive Cotton effect of VIb has now been published.[5]

[3] C. Djerassi and A. E. Lippman, *J. Amer. Chem. Soc.* **77**, 1825 (1955).
[4] L. H. Briggs, Personal communication.
[5] C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **81**, 2386 (1959).

Unequivocal proof of the structure of phyllocladene must ultimately rest on the establishment of relationship to a substance of known absolute stereochemistry. The most likely compound for this comparison would seem to be unsaturated ketone XIII derived from manool. With this in mind the silver salt of V was subjected to a Hunsdiecker degradation, but the only product isolated was the lactone XII. This substance was also formed as a sole product by treatment of VIa with sodium borohydride, when the carboxylate anion must control the stereochemistry of the reduction. It was thought likely that pyrolysis of the acetate of V would lead to elimination of acetic acid, possibly followed by decarboxylation, but the lactone XII was again produced by this procedure in high yield.

This correlation has been established by the following sequence of reactions. The dioxime of the keto-aldehyde (III), on treatment with acetic anhydride yielded XIVa, which deacetylated during chromatography on alumina giving XIVb. The parent keto-nitrile (XIVc) was regenerated and subjected to the action of pertrifluoroacetic acid. After hydrolysis, the β-hydroxy-nitrile XV was produced. This did not melt sharply and was almost certainly a mixture of 13-hydroxy isomers, epimerization taking place during the preceding reactions. Oxidation of the mixture gave 8β-cyano-13-oxopodocarpane (XVI) as sole product. When this substance was distilled under vacuum from powdered potassium hydroxide, hydrogen cyanide was eliminated, giving 13-oxopodocarp-8(14)-ene (XIII), identical with a sample prepared from manool.[6]

Hence isophyllocladene must possess the "normal" *trans* A/B ring junction, since the reactions described above do not permit the possibility of inversion at these centres. As Djerassi[5] has already pointed out that only one structure possessing this ring fusion is permitted by rotatory dispersion evidence, isophyllocladene must be represented by I.

EXPERIMENTAL

Rotations were measured in chloroform at room temp unless otherwise stated. M.p's were taken on a Kofler block and are corrected. The alumina used for chromatography had activity II. Light petroleum refers to the fraction with b.p. 60–80°.

Dihydro-15, 16-*dihydroxyphyllocladene* (II). Isophyllocladene (480 mg) was allowed to react with osmium tetroxide (460 mg) in ether (50 ml) and pyridine (5 ml) for 24 hr at 0°. The solution was then saturated with hydrogen sulphide, filtered, and the product crystallized from benzene as flat needles (420 mg) of dihydro-15,16-dihydroxyphyllocladene, m.p. 234–235°, with sublimation (lit,[1] m.p. 235°), $[\alpha]_D$ +7° (*c*, 0·6). (Found: C, 78·1; H, 11·0. $C_{20}H_{34}O_2$ requires: C, 78·4; H, 11·2%.)

Chromic acid oxidation of dihydro-15,16-*dihydroxyphllocladene*. II (320 mg) in acetone (100 ml) was oxidized with 8N chromic acid/sulphuric acid in the usual way.[7] The product was adsorbed from light petroleum–benzene (1 : 1) on alumina (50 g). Elution with benzene gave the unsaturated D-homo-*ketone* (VIII) as needles from aqueous methanol, m.p. 115–115·5° $[\alpha]_D$ −152° (*c*, 1·2). (Found: C, 83·85; H, 10·6. $C_{20}H_{30}O$ requires: C, 83·85; H, 10·55%). Further elution with ether gave *dihydro*-16-*hydroxy*-15-*oxophyllocladene* (VII) as needles (40 mg) from aqueous methanol, m.p. 144–146°. (Found: C, 76·6; H, 10·15. $C_{20}H_{32}O_2 \cdot \frac{1}{2}CH_3OH$ requires: C, 76·8; H, 10·7%.) Infra-red absorption in CCl_4 at 1734 cm^{-1}.

Wolff–Kishner reduction of VIII. The D-*homo*-ketone (VIII, 60 mg) was heated under reflux with diethylene glycol (20 ml) and hydrazine (1 ml, 95%) for 1 hr. Potassium hydroxide (2 g) was then added and the temp of the solution raised to 205° by distillation. The reaction was maintained at this temp for 12 hr, the product extracted with light petroleum and crystallized from methanol as needles

[6] J. R. Hosking, *Ber. Dtsch. Chem. Ges.* **69**, 780 (1936).
[7] A Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2543 (1953).

(45 mg) of IX, m.p. 92–93·5°, $[\alpha]_D$ −14·5° (*c*, 1·2). (Found: C, 88·5; H, 11·5. $C_{20}H_{32}$ requires: C, 88·15; H, 11·85%.) D-homo-*dihydrophyllocladene* (X). IX (12·1 mg) was hydrogenated using Adams' catalyst in acetic acid. The product crystallized as needles (11 mg) of X from methanol, m.p. 118–119°, $[\alpha]_D$ +4° (*c*, 0·9). (Found: C, 87·7; H, 12·2. $C_{20}H_{34}$ requires: C, 87·5; H, 12·5%).

13β-*Acetyl*-8β-*aldehydopodocarpane* (III). The diol II (308 mg) was heated under reflux with lead tetracetate (750 mg) in benzene (100 ml) for 1 hr. The mixture was then poured into water, the product extracted with benzene and crystallized from light petroleum as long plates (195 mg) of 13β-*acetyl*-8β-*aldehydopodocarpane*, m.p. 138–140°, $[\alpha]_D$ −39° (*c*, 0·9). (Found: C, 79·15; H, 10·6. $C_{20}H_{32}O_2$ requires: C, 78·9; H, 10·6%.) Infra-red absorption in CCl_4 at 1713 (C=O), 2847 and 2869 cm^{-1} (C—H).

Chromic acid oxidation of III. III (709 mg) in acetic acid (70 ml) was allowed to react with chromium trioxide (185 mg) for 12 hr. The acidic product (210 mg) was separated and the neutral material (480 mg) treated as before with chromium trioxide. This process of oxidation was repeated (usually 3 times in all) until the acid being formed was no longer crystalline. The combined acidic fractions were dissolved in methanol containing 10% of hydrochloric acid and heated under reflux for 3 hr. The product was adsorbed from benzene on silica gel (100 g) and eluted with benzene–chloroform (2 : 3) as plates (340 mg) of 13α-acetyl-8β-carboxypodocarpane (IV) from light petroleum–chloroform, m.p. 174·5–175° (lit,[1] m.p. 176°), $[\alpha]_D$ −26° (*c*, 1·3). (Found: C, 75·25; H, 10·15. $C_{20}H_{32}O_3$ requires: C, 74·95; H, 10·05%.) Further elution with chloroform–methanol (19 : 1) gave another acid (20 mg) from light petroleum, m.p. 185–186°, undepressed on admixture with an authentic specimen of VIa.

The residual neutral material from the oxidation was adsorbed from light petroleum on alumina. Elution with benzene gave 13α-*acetyl*-8β-*aldehydopodocarpane* (XI) as plates (12 mg) from aqueous methanol, m.p. 84·5–86°, $[\alpha]_D$ −14° (*c*, 0·8). Found: C, 78·55; H, 11·0. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%.)

Cyclization of the keto-aldehydes (III) *and* (XI). Chromatography of III on alumina brought about partial formation of the unsaturated ketone VIII. Complete cyclization was accomplished by treatment with methanolic potassium hydroxide (5%) for 3 hr at room temp. XI required to be heated under reflux for 1 hr with methanolic potassium hydroxide (10%) to affect cyclization.

Oxidation of 13α-*Acetyl*-8β-*carboxypodocarpane* (IV). IV (149 mg) in methylene chloride (1 ml) was added dropwise to a stirred solution of pertrifluoroacetic acid, prepared from trifluoroacetic anhydride (0·145 ml) and hydrogen peroxide (0·02 ml) in methylene chloride (3 ml) at 0°. The mixture was maintained at 0° for 10 min and then heated under reflux for 30 min. The product, after hydrolysis with methanolic potassium hydroxide (10%, 1 hr under reflux) was adsorbed from benzene–chloroform (1 : 1) on silica gel (20 g) and eluted with chloroform–methanol (19 : 1). Crystallization from light petroleum–ethanol gave needles (80 mg) of 8β-*carboxy*-13α-*hydroxypodocarpane* (Va), m.p. 280–282° with sublimation, $[\alpha]_D$ −26° (*c*, 0·6 in MeOH). (Found: C, 73·75; H, 9·85. $C_{19}H_{30}O_3$ requires: C, 73·45; H, 10·25%.)

Methylation of the above acid with ethereal diazomethane gave the corresponding methyl ester Vb as an uncrystallizable oil.

8β-*Carbomethoxy*-13-*oxopodocarpane* (VIb). The methyl ester Vb (30 mg) in acetone (10 ml) was oxidized with 8 N chromic acid/sulphuric acid. The product crystallized from chloroform–light petroleum as prisms (25 mg) of VIb, m.p. 159–161°, $[\alpha]_D$ −15° (*c*, 1·4). (Found: C, 74·7; H, 9·8. $C_{19}H_{30}O_3$ requires: C, 74·45; H, 9·85%.)

8β-*Carboxy*-13-*oxopodocarpane* (VIa). The methyl ester VIb (11·8 mg) was heated under reflux with 20% aqueous methanol (7 ml) containing sodium hydroxide (2%) for 14 hr. After this time approx 80% of the ester had been hydrolysed. (Under identical hydrolysis conditions the methyl ester Vb was recovered unchanged.) The acidic product was crystallized from light petroleum–chloroform as needles (8 mg) of VIa, m.p. 185–186° with sublimation (lit[1] m.p. 182–183°), $[\alpha]_D$ −23° (*c*, 0·5). (Found: C, 73·7; H, 9·4. $C_{19}H_{28}O_3$ requires: C, 73·95; H, 9·65%.) This same acid was also prepared by oxidation of Va with chromic acid.

Hunsdiecker reaction on silver salt of (Va). The silver salt (236 mg) of the hydroxy-acid Va was suspended in dry carbon tetrachloride (100 ml) maintained under reflux. Bromine (0·033 ml) in CCl_4 was added and the heating continued for 5 min till the bromine colour had disappeared. The neutral product was sublimed and crystallized as needles (85 mg) of the *lactone* XII from methanol, m.p. 151–152°, $[\alpha]_D$ +1° (*c*, 0·7). (Found: C, 78·15; H, 10·1. $C_{19}H_{28}O_2$ requires: C, 78·2; H, 10·2%.)

Infra-red absorption in $CHCl_3$ at 1778 cm^{-1}. From the acidic fraction, Va (78 mg) was recovered.

Pyrolysis of the acetate of (Va). The hydroxy-acid Va (28 mg), acetic anhydride (0·2 ml) and pyridine (0·4 ml) were allowed to react at room temp for 18 hr. The solvents were removed under vacuum at 40°, the product dissolved in benzene and adsorbed on silica gel (20 g). Elution with benzene–chloroform (1 : 3) gave the acetate of Va as an oil which could not be crystallized. This oil was heated, under nitrogen, with copper bronze (50 mg) for 15 min at 250–260°. On cooling, the mixture solidified. Sublimation gave the lactone XII (21 mg).

Reduction of the 8β-carboxy-13-oxopodocarpane (VIa). VIa (45 mg) in 50% aqueous methanol (15 ml) was allowed to react with sodium borohydride (70 mg) for 12 hr. After acidification the neutral product (21 mg) crystallized as needles from aqueous methanol, m.p. 151–152° undepressed on admixture with the lactone XII. Chromatography of the acidic fraction on silica gel gave unchanged VIa (20 mg).

Oxime of 13β-acetyl-8β-cyanopodocarpane (XIVb). 13β-Acetyl-8β-aldehydopodocarpane (1·14 g), hydroxylamine hydrochloride (2 g), pyridine (1·5 ml) and ethanol (20 ml) were heated together under reflux for 1 hr. The crude dioxime (850 mg), isolated by precipitation with water and crystallization from aqueous methanol, had m.p. 192–199°. This material was heated under reflux with acetic anhydride (15 ml) and sodium acetate (1 g) for 1 hr. Isolation, as above, gave a product which absorbed at 1730 cm^{-1}, indicating the presence of an acetate, XIVa. This substance was adsorbed from benzene on alumina (50 g) and eluted with ether–methanol (19 : 1) as prisms (505 mg from light petroleum–chloroform) of XIVb, m.p. 195–197° with sublimation, $[\alpha]_D$ −13° (*c*, 0·8). (Found: C, 75·75; H, 10·0; N, 9·15. $C_{20}H_{27}ON_2$ requires: C, 75·9; H, 10·2; N, 8·85%.)

13-Acetyl-8β-cyanopodocarpane (XIVc). A solution of sodium nitrite (460 mg) in water (1·5 ml) was added to XIVb (460 mg) in acetic acid (10 ml) and the mixture maintained at room temp for 4 hr. The crystalline product, isolated in the usual manner, appeared to be a mixture of the expected ketone and the nitrimine.[5] It was dissolved in dioxane–water (25 ml, 4 : 1) and heated on a steam bath for 2 hr. Dilution with water and extraction with ether gave a substance which was adsorbed on alumina (30 g) from light petroleum–benzene (1 : 1) and eluted with benzene–ether (9 : 1) as needles (175 mg from aqueous methanol) of *13-acetyl-8β-cyanopodocarpane*, m.p. 102–104° with softening at 96–100°. (Found: C, 79·9; H, 10·85; N, 4·45. $C_{21}H_{31}ON$ requires: C, 79·65; H, 10·35; N, 4·65%.)

8β-Cyano-13-hydroxypodocarpane (XV). 13-Acetyl-8β-cyanopodocarpane (158 mg) was oxidized with pertrifluoroacetic acid in the presence of anhydrous disodium hydrogen phosphate (400 mg) in the manner previously described. The product, after hydrolysis with methanolic potassium hydroxide (2%, 1 hr under reflux) was adsorbed from benzene on alumina (20 g). Elution with ether–methanol (9 : 1) gave XV as needles (85 mg) from light petroleum–chloroform, m.p. 95–115°. (Found: C, 78·8; H, 10·85. $C_{18}H_{29}ON$ requires: C, 78·5; H, 10·6%.)

8β-Cyano-13-oxopodocarpane (XVI). 8β-Cyano-13-hydroxypodocarpane (68 mg) in acetone (10 ml) was oxidized with 8N chromic acid/sulphuric acid. The product was adsorbed from benzene on alumina (10 g) and eluted with benzene–ether (4 : 1) as needles (42 mg from chloroform–light petroleum) of XVI, m.p. 160–161° with prior melting and resolidification at 153–154·5°, $[\alpha]_D$ +33° (*c*, 0·6). (Found: C, 78·85; H, 9·7. $C_{18}H_{27}ON$ requires: C, 79·05; H, 9·95%.)

13-Oxopodocarp-8(14)-ene (XIII). 8β-Cyano-13-oxopodocarpane (15 mg) was mixed with powdered potassium hydroxide (150 mg) and the mixture distilled at 120° (0·01 mm). The product was adsorbed on alumina (5 g) from light petroleum and eluted with benzene–ether (9 : 1) as prisms (6 mg from methanol) of XIII, m.p. 64–66°, $[\alpha]_D$ +45° (*c*, 0·4), λ_{max} (MeOH) 242·5 mμ, ε = 16,000. A specimen of the same material prepared from manool had m.p. 64–66° (undepressed on admixture with XIII), $[\alpha]_D$ +49° (*c*, 0·9), λ_{max} (MeOH) 242·5 mμ, ε = 16,400.

The infra-red spectra of the two samples in CCl_4 were identical.

Acknowledgements—We wish to thank Professor R. A. Raphael for his help and encouragement, and Professors C. Djerassi and L. H. Briggs for communicating the results of their experiments prior to publication. We are also indebted to Professor C. Djerassi for determining the rotatory dispersion curve of VIb.

[5] S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney and L. J. Wyman, *J. Chem. Soc.* 4614 (1958).

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THE CHEMISTRY OF PORPHYRIN *a*

POSITION OF THE FORMYL GROUP

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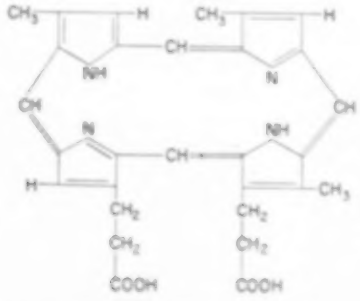
Abstract—Porphyrin *a* was transformed into the corresponding nitrile, which was oxidized with potassium permanganate. 3-Cyano-4-propionic-2,5-pyrroledicarboxylic acid was identified among the degradation products by chromatographic comparison with the same acid obtained by synthesis. This result shows that the formyl group is present in position 8.

A new synthesis of "cytopyrrolic acid" (III), a peculiar oxidation product of porphyrin *a*, is also described.

IDENTIFICATION of 3-methyl-2,4,5-pyrroletricarboxylic (I) 3-methyl-4-propionic-2,5-pyrroledicarboxylic (II) and 3-propionic-2,4,5-pyrroletricarboxylic (III) acids, degradation products from porphyrin *a* with $KMnO_4$, has been previously described.[1,2]

3-Propionic-2,4,5-pyrroletricarboxylic acid, not found before by degradation of natural porphyrins, was called "cytopyrrolic acid" and its structure was demonstrated by synthesis.[3] These results and the quantitative determination of carboxyl groups[4] (only two are present, obviously those of the propionic side chains), indicate that three readily oxidizable groups are present in porphyrin *a*.

At the same time, the structure of cytodeuteroporphyrin, first obtained by Warburg and Gewitz[5] from haemin *a* by the resorcinol melt, was proved by synthesis;[6] its formula is as follows:



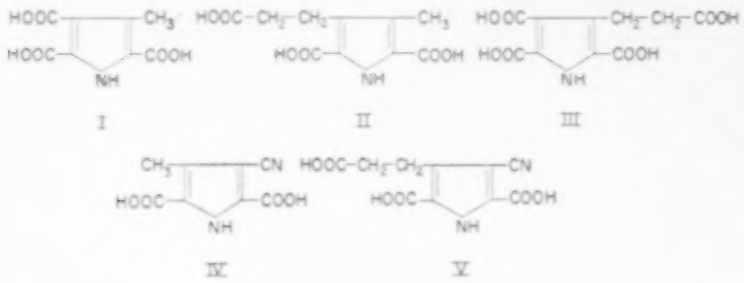
The sequence of pyrrole rings was therefore elucidated; but the nature of the substituents at positions 2, 4, and 8 still remained obscure.

Since there was strong evidence for a formyl group, based on the reaction of haemin *a* with cysteine,[7] hydroxylamine and hydrazine[8] and on spectroscopically

[1] M. Piattelli and R. A. Nicolaus, *Rend. Acc. Sc. fis. e mat.* (Ser. 4ª), **XXVI** 44 (1959).
[2] M. Piattelli and R. A. Nicolaus, *Rend. Acc. Sc. fis. e mat.* (in press).
[3] M. Piattelli, *Rend. Acc. Sc. fis. e mat.* (in press).
[4] O. Warburg and H. S. Gewitz, *Z. Physiol. Chem.* **288**, 1 (1951).
[5] O. Warburg and H. S. Gewitz, *Z. Physiol. Chem.* **292**, 174 (1953).
[6] G. S. Marks, D. K. Dougall, E. Bullock and S. F. McDonald, *J. Amer. Chem. Soc.* **81**, 250 (1959).
[7] W. A. Rawlinson and J. H. Hale, *Biochem. J.* **45**, 247 (1949).
[8] R. Lemberg and J. E. Falk, *Biochem. J.* **49**, 674 (1951).

observed conversion of an aldoxime to a nitrile,[9] attempts were made to ascertain the existence of the formyl by chemical methods and possibly to determine its position.

Porphyrin *a* was, therefore, transformed into oxime and this was dehydrated to nitrile by boiling with acetic anhydride; the product was oxidized with alkaline $KMnO_4$ and comparison of the mixture of degradation products with samples of acids I, II, III, IV, and V was made by paper chromatography.



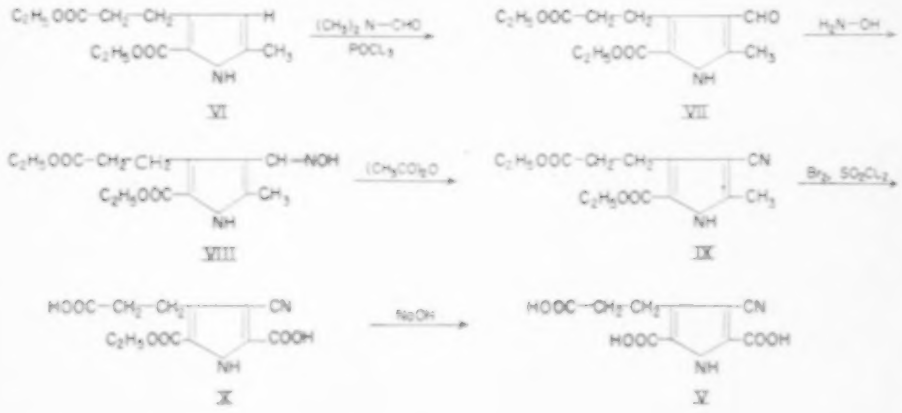
I II III

IV V

Only the acids I, II, III and V were actually identified.

This result shows that a formyl group is really present in porphyrin a, *and is in position* 8.

The acid V was synthesized as follows:



VI VII

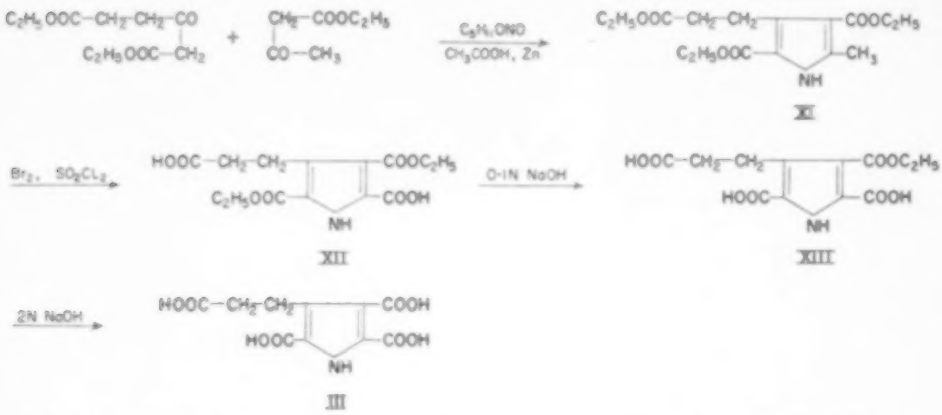
VIII IX

X V

The pyrrole VI, prepared according to MacDonald,[10] was formylated with dimethylformamide and phosphorus oxychloride to give the aldehyde VII, m.p. 120–121°, this procedure being easier than that of Gattermann. By reaction of the aldehyde VII with hydroxylamine, the oxime VIII, m.p. 141–142° was obtained, which was dehydrated to the nitrile IX, m.p. 128–129° by boiling with acetic anhydride. This compound reacted with bromine and sulphuryl chloride in acetic acid, affording the ester X, m.p. 245–246°. The hydrolysis of X to the acid V, m.p. 272–273°, was achieved by boiling with 2 N sodium hydroxide.

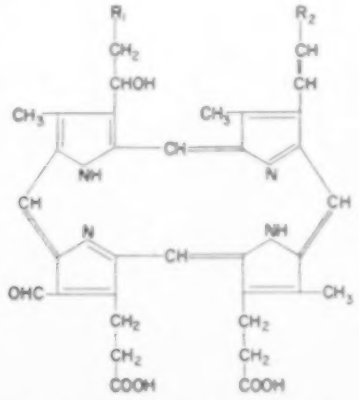
[9] H. Dannenberg and M. Kiese, *Biochem. Z.* **322**, 395 (1952).
[10] S. F. MacDonald, *J. Chem. Soc.* 4176 (1952).

Further proof of the structure of V was also obtained. This compound was subjected to prolonged alkaline hydrolysis, giving "cytopyrrolic acid" III. This acid was previously synthesized;[3] a new easier method has been worked out which is summarized in the following scheme:



Ethyl β-ketoadipate, prepared according to Eisner *et al.*[11] and MacDonald,[10] was converted into the oximine derivative which was condensed with ethyl acetoacetate to give the pyrrole XI, m.p. 94–95°. After reaction of XI with bromine and sulphuryl chloride, the diester XII, m.p. 198–199°, was obtained. The selective saponification of one of the ester groups, achieved with 0·1 N sodium hydroxide, gave a monoester, which melted at 227–228° alone or admixed with an authentic specimen of XIII. Further hydrolysis of the ester XIII with 2 N sodium hydroxide yielded the acid III.

On the basis of the most recent information on the structure of porphyrin *a*[12,13] and on the evidence that the formyl group and the unsaturated side chains (postulated by Warburg and Gewitz,[4] relying upon the hydrogen uptake in the catalytical reduction of haemin *a* in borate buffer) are very likely on opposite pyrroles,[8] the formula of porphyrin *a* can be written as follows:



[11] U. Eisner, J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.* 2223 (1950).
[12] P. S. Clezy and J. Barrett, *Biochim. Biophys. Acta* **33**, 584 (1959).
[13] J. Barrett, *Nature, Lond.* **183**, 1185 (1959).

where R_1 and R_2 are alkyl groups (or eventually hydrogen). Our present work calls for definite proofs that structures of the substituents at positions 2 and 4, as formulated above, are really correct (this is highly probable but yet uncertain) and to elucidate the distribution between them of about twelve more carbon atoms, resulting from elementary analysis.

Preliminary experiments, performed by catalytical reduction of porphyrin *a* followed by permanganate oxidation, have not shown the presence, in the mixture of degradation products, of 4-ethyl-3-methyl-2,5-pyrroledicarboxylic acid: this is a normal oxidation product of mesoporphyrin IX, phaephorbide *a* and all related compounds having a β-methyl-β'-ethyl substituted pyrrolic nucleus.[14] This result shows that R_2 at least is not hydrogen.

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EXPERIMENTAL

M.p. are not corrected.

Paper chromatograms were run on Whatman No. 1 filter paper (descending development); after drying, they were sprayed with the diazonium salt of sulphanilic acid and with N sodium hydroxide.

5-Carbethoxy-4,2'-carbethoxyethyl-2-methylpyrrole-3-aldehyde (VII). Phosphorus oxychloride (4 ml) was added at 20° to a stirred solution of the pyrrole VI (5 g) in dimethylformamide (2 ml). The mixture was heated for 2 hr at 100°, then cooled, poured into water (100 ml) and sodium acetate trihydrate was added until pH 4 was reached. After 4 hr the light brown precipitate was filtered off, washed and crystallized from water (charcoal) to give 2·15 g (38·6%) of VII, m.p. 120–121°.

5-Carbethoxy-4,2'-carbethoxyethyl-2-methylpyrrole-3-aldoxime (VIII). Aldehyde VII (1·45 g), hydroxylamine hydrochloride (3·5 g), 10% sodium hydroxide solution (14 ml) and just sufficient ethanol to give a clear solution were heated under reflux for 10 min. After cooling the product was filtered off, washed with water and dried. Crystallized from ethanol, it formed colourless prisms (1·22 g, 79·9%), m.p. 141–142° (Found: C, 56·84; H, 6·72. $C_{14}H_{20}O_5N_2$ requires: C, 56·74; H, 6·80%). Ehrlich's reaction was positive in the hot.

5-Carbethoxy-4,2'-carbethoxyethyl-2-methylpyrrole-3-nitrile (IX). The oxime VIII (1 g) was refluxed for 4 h with acetic anhydride (35 ml) and anhydrous sodium acetate (1 g). Acetic anhydride was removed under reduced pressure and the brown residue was suspended in water, filtered off, washed and dried. The crude product, crystallized from light petroleum (b.p. 80–100°; 250 ml), afforded pure IX (0·75 g, 79·8%) in long, colourless needles, m.p. 128–129° (Found: C, 60·41; H, 6·34. $C_{14}H_{18}O_4N_2$ requires: C, 60·42; H, 6·52%). Ehrlich's reaction was positive in the hot.

5-carbethoxy-3-cyano-4-propionic-2-pyrrolecarboxylic acid (X). The nitrile IX (0·5 g) was dissolved in acetic acid (5 ml) containing acetic anhydride (0·3 ml); bromine (0·1 ml) and sulphuryl chloride (0·7 ml) were added to the solution, at about 15°. The mixture was allowed to stand at 4° overnight, and after addition of water (4 ml) heated at 60° for 20 min. After cooling, more water was added (100 ml) and the solution was extracted with ether (100 ml in four portions). The extracts were dried over magnesium sulphate, and the ether was removed by distillation under reduced pressure, leaving the crude product. After three recrystallizations from ethyl acetate, colourless needles (0·175 g, 34·8%), m.p. 245–246°, were obtained, which did not give Ehrlich's reaction (Found: C, 51·42; H, 4·33. $C_{12}H_{12}O_6N_2$ requires: C, 51·43; H, 4·32%). Analytical data revealed that this compound was a monoester, not the expected diester; with the diazonium salt of sulphanilic acid a yellow colour was obtained, which indicated that an α-carboxylic group was still esterified;[15] therefore it was formulated as X.

3-Cyano-4-propionic-2,5-pyrroledicarboxylic acid (V). The ester X (0·1 g) was heated under reflux for 1 hr with 2N NaOH (2 ml). After cooling at 0°, the clear solution was acidified and extracted with ether (40 ml in four portions). The extracts were dried over magnesium sulphate, and the ether removed *in vacuo*. The residual crystalline material (78 mg) was analyzed by paper chromatography: beside the acid V, it contained traces of 3-propionic-2,4,5-pyrroletricarboxylic acid III and little amounts of another pyrrole derivative (probably the corresponding amide). Crystallization from acetic acid gave the pure acid V (60 mg, 66·7%) as colourless needles, m.p. 272–273° (Found: C,

[14] R. A. Nicolaus, L. Mangoni and L. Caglioti, *Annali di Chim.* **46**, 793 (1956).
[15] R. A. Nicolaus and L. Mangoni, *Annali di Chim.* **46**, 847 (1956).

47·41; H, 3·25. $C_{16}H_8O_6N_2$ requires: C, 47·62; H, 3·20%). Ehrlich's reaction was negative; with the diazonium salt of sulphanilic acid in alkaline solution it gave a bright red colour. Prolonged hydrolysis (12 hr under reflux) of V with 2N NaOH gave 3-propionic-2,4,5-pyrroletricarboxylic acid, identified by paper chromatography.

3,5-Dicarbethoxy-4,2'-carbethoxyethyl-2-methylpyrrole (XI). Ethyl β-ketoadipate (12 g) containing conc HCl (0·2 ml) was treated with amyl nitrite (6·5 g) during 1 hr at 30–35°. The resulting solution was set aside at room temp overnight and then run during 1 hr into a vigorously stirred mixture of acetic acid (65 ml), ammonium acetate (8 g), ethyl acetoacetate (7·15 g) and zinc dust (3·2 g) at 60–65°; at the same time zinc dust (8·5 g) was added in small portions. The mixture was then heated for 3 hr at 100°, the hot solution decanted from zinc into stirred ice-water (600 ml), and the zinc washed with hot acetic acid. The product was filtered off, washed with water and crystallized from dilute ethanol, giving 10 g (55·4%) of colourless needles, m.p. 94–95° (Found: C, 58·90; H, 7·16. $C_{16}H_{23}O_6N$ requires: C, 59·06; H, 7·13%). Ehrlich's reaction was positive in the hot.

3,5-dicarbethoxy-4-propionic-2-pyrrolecarboxylic acid (XII). Bromine (1·1 ml) and sulphuryl chloride (6·8 ml) were added to a solution of the pyrrole XI (6 g) in acetic acid (40 ml) containing acetic anhydride (2 ml), at 15°. The mixture was allowed to stand overnight at 4°, water was added until it became slightly turbid and then heated at 60° for 20 min. After cooling, water was added to a total volume of 300 ml; the crude product was filtered off, washed and crystallized from dioxane–water mixture, yielding 3·7 g (61·3%) of m.p. 198–199° (colourless plates). Ehrlich's reaction was negative (Found: C, 51·56; H, 5·18. $C_{14}H_{17}O_8N$ requires: C, 51·37; H, 5·24%). Analysis proved that the compound obtained was a diester instead of the expected triester. With the diazonium salt of sulphanilic acid, a yellow colour was obtained: this demonstrated that an α-carboxylic group was still esterified. On the other hand, its partial hydrolysis with a slight excess of 0·1N NaOH for 15 min at 100° afforded a monoester which, after crystallization from acetic acid, had m.p. 227–228°, undepressed when mixed with an authentic specimen of 3-carbethoxy-4-propionic-2,5-pyrroledicarboxylic acid (XIII). The identity of these two compounds was confirmed by paper chromatography. The structure of the ester XII was thus proved. Hydrolysis of the monoester XIII with excess of 2N NaOH as described elsewhere,[3] gave 3-propionic-2,4,5-pyrroletricarboxylic acid.

Action of hydroxylamine on porphyrin a, *dehydration with acetic anhydride and subsequent oxidation*

Porphyrin *a*, prepared according to Lemberg[16,17] (15 mg) was added to a solution of hydroxylamine hydrochloride (15 mg) in pyridine (1 ml). After 10 min, ether was added (200 ml), and pyridine removed by washing first with N HCl and then with water. The washed ether solution, dried over sodium sulphate, was evaporated to dryness under reduced pressure. Acetic anhydride (10 ml) and anhydrous sodium acetate (0·2 g) were added to the solid residue, and the mixture was refluxed for 30 min. Acetic anhydride was removed by heating on a steam-bath *in vacuo* and the residue suspended in water, filtered off and washed. The product was oxidized without any further purification: it was suspended in 2N K_2CO_3 (1 ml) and oxidized by gradual addition of a saturated solution of potassium permanganate. When the colour of the permanganate persisted for 10 min (1·5 ml were needed), the resulting mixture was briefly boiled, the manganese dioxide filtered off and washed twice with hot distilled water (2 ml). Combined filtrate and washings were adjusted to pH 4–4·5 with HCl and 20% calcium chloride solution (0·2 ml) was added. After 1 hr, the precipitate was removed by filtration, the clear filtrate made acidic to Congo red and extracted with ether (20 ml in five portions). The extracts, dried over magnesium sulphate, were evaporated to dryness. Distilled water (0·1 ml) was added to the residue and the filtered solution was used for paper chromatography.

Chromatograms were run with n-butanol: acetic acid: water (60 : 15 : 25) (R_f value for V is 0·70) or ethanol: 33% NH_3: water (80 : 4 : 16) (R_f value for V is 0·46) as solvents, and the acids I, II, III and V were detected.

3-Propionic-2,4,5-pyrroletricarboxylic acid was always present in remarkable amounts: this is difficult to explain and could be due either to incomplete reaction of porphyrin *a* with hydroxylamine or to previous oxidation of the formyl group of porphyrin *a*. It cannot be accounted for by hydrolysis of the cyano group of V in alkaline solution, because this reaction is very slow at room temperature.

The same results were obtained with haemin *a*, prepared according to Warburg and Gewitz.[18]

[16] R. Lemberg, *Nature, Lond.* **172,** 619 (1953).
[17] R. Lemberg, D. B. Morell, W. H. Lockwood, M. Stewart and B. Bloomfield, *Chem. Ber.* **89,** 309 (1956).
[18] O. Warburg, H. S. Gewitz and V. Völker, *Z. Naturf.* **10b,** 541 (1955).

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CONTRIBUTION A L'ETUDE DES COMPOSES SESQUITERPENIQUES—IV

ETUDE DE LA STRUCTURE DU CAROTOL, ALCOOL $C_{15}H_{26}O$ DE L'ESSENCE DE *DAUCUS CAROTA**

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Résumé—La structure du carotol, alcool tertiaire monoéthylénique sesquiterpénique $C_{15}H_{26}O$ de l'essence de graines de *Daucus Carota*, a été déterminée conjointement par des méthodes chimiques et par spectroscopie infra-rouge.

Cette étude montre que la formule décalanique ci-après, proposée par Sorm et Urbanek, en 1948, est erronée. *Le carotol est en fait le* Δ^2*-3,10-diméthyl-6-isopropylbicyclo-(0,3,5)-décèn-6-ol* (I).

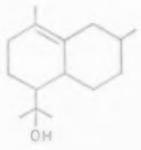
Abstract—The structure of carotol, the sesquiterpenoid monoethylenic tertiary alcohol $C_{15}H_{26}O$, extracted from the essential oil of *Daucus Carota*, has been determined using both chemical methods and infra-red spectroscopy.

This study shows that the decalanic formula proposed in 1948 by Sorm and Urbanek is erroneous. *Carotol is in fact* Δ^2*-3,10-dimethyl-6-isopropylbicyclo-(0,3,5)-decen-6-ol* (I).

I

LE carotol est un alcool tertiaire monoéthylénique sesquiterpénique de formule brute $C_{15}H_{26}O$. Il a été isolé pour la première fois en 1925 par Asahina et Tsukamoto[1] à partir de l'essence de graines de *Daucus Carota*.† Depuis lors, le carotol a été décelé dans plusieurs végétaux, tel Seseli tortuosum,[2]† tous des ombellifères. Il semble, donc, être caractéristique de cette famille.

L'étude du carotol a été abordée par Asahina et poursuivie par Palfray et Lepesqueur.[3] Il faut cependant attendre 1948 pour voir Sorm et Urbanek[4] proposer pour le carotol la formule ci-après, au squelette nouveau dans la série des sesquiterpènes.



* Précédente communication: *Tetrahedron* **4**, 1 (1958).
† Cette essence contient une trentaine de pourcents de carotol.

[1] Y. Asahina et J. Tsukamoto, *J. Pharm. Soc. Japan* **525**, 1 (1925); *Ibid.* **525**, 961 (1925).
[2] R. Salgues, *C.R. Acad. Sci., Paris* **241**, 677 (1955).
[3] L. Palfray, A. M. Lepesqueur, *C.R. Acad Sci., Paris* **198**, 1365 (1934).
[4] F. Sorm et L. Urbanek, *Coll. Czechosl. Chem. Comm.* **13**, 49 (1948); *Ibid.* **13**, 420 (1948).

Sorm et Urbanek ont pratiqué un nombre d'expériences très limité et la structure qu'ils attribuent au carotol repose, essentiellement, sur leur interprétation des résultats d'une déshydrogénation de cet alcool: obtention du 1,7-diméthyl-4-isopropyl-naphtalène.[a]

Cette interprétation est assez inattendue car, à côté de ce naphtalénique, le déshydrogénat renferme une fraction azulénique non identifiée. Or, une étude approfondie de la littérature sur les données de la déshydrogénation permet de tirer une règle suivant laquelle la présence, dans un déshydrogénat, d'un azulénique, même accompagné d'un naphtalénique, est le reflet d'une structure hydroazulénique du sesquiterpène de départ. Un sesquiterpène de structure décalanique ne donne qu'un naphtalénique.

La formule proposée par Sorm pour le carotol, est donc sujette à caution.

ETUDE DE LA STRUCTURE DU CAROTOL ALCOOL SESQUITERPENIQUE $C_{15}H_{26}O$ DE L'ESSENCE DE DAUCUS CAROTA

I. *Carotol et ses dérivés*

1. *Source et séparation du carotol*

L'huile essentielle brute que nous avons traitée pour en extraire le carotol est de même provenance que celle utilisée par Sorm et Urbanek. C'est une essence de graines de *Daucus Carota* pratiquement débarrassée de monoterpènes et présentant les constantes physiques suivantes (entre parenthèses les données de Sorm et Urbanek[4]):

$$d_4^{20} = 0{,}9539\ (0{,}9511); \qquad n_D^{20} = 1{\cdot}4890\ (-)$$

$$[\alpha]_D^{20} = +2°46\ (+1°2)$$

Le carotol, seul alcool sesquiterpénique de l'huile, étant présent en quantité importante (25%), sa séparation, par distillation fractionnée, n'offre pas de difficultés. Une partie du distillat a été ensuite soumise à une purification par chromatographie, ceci afin d'obtenir un échantillon très pur de carotol en vue d'en relever le spectre et les constantes. Le carotol est une substance huileuse, très légèrement colorée en jaune. Une trace de cette substance étendue sur la peau ou sur papier filtre laisse une odeur agréable et fraîche de carotte.

2. *Constantes physiques du carotol et de ses dérivés caractéristiques*

L'identité de notre échantillon de carotol avec ceux étudiés par Sorm[4] et par Vanderlinden[5] s'établit par comparaison des valeurs de ses constantes et des points de fusion des dérivés solides caractéristiques: daucol (II) et carotanetriol (III). Ceux-ci s'obtiennent respectivement par époxydation et par hydroxylation de la double liaison du carotol.

3. *Carotane* (IV)[5]

En présence du noir de platine, le carotol absorbe à la température du laboratoire, deux moles d'hydrogène pour donner le carotane (IV).

La réduction de la double liaison du carotol s'accompagne donc de l'hydrogénolyse

[a] Notons, en passant, que ce naphtalénique est isolé également des déshydrogénats de l'acorone et d'un dérivé laserpitinique: le laséro1.

[5] F. Vanderlinden, Dissertation, Université Libre de Bruxelles (1957).

TABLEAU 1. CONSTANTES PHYSIQUES DU CAROTOL (I) DU DAUCOL (II) ET DU CAROTANETRIOL (III)

Carotol (I)					Daucol (II)	Carotane-triol (III)	Auteurs
Eb.$_{0\cdot3}$	d_4^{20}	n_D^{20}	$[\alpha]_D^{20}$	$R\,M_D$ obs (calc 68·13)	F	F	
	0·9660	1·4987	+28°		118°	142°	Asahina et Tsukamoto[1]
	0·960	1·498	+27°				Palfray et Lepesqueur[2]
97°–98°	0·9660	1·4985	+29°6	67·48	118°	142°	Sorm et Urbanek[4]
						141°5	Salgues[5]
97°–97,5°	0·9661	1·4987	+29°4	67·50	118°	141°	Vanderlinden[3]
	0·9660	1·4985	+29°6	67·45	118°	142°	Ce travail

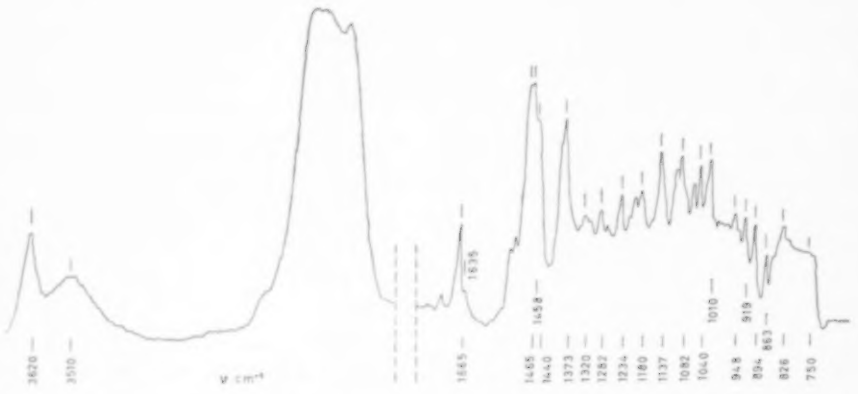


FIG. 1. Spectre du carotol (0,681 g + 2 ml CCl_4) Spectrogr. Hilger H 800, prisme NaCl, cell. ép. 0,01 cm. Fente 0,36 à 1000 cm^{-1}; progrm 30, ampl 4, supress 25; came R_2; vitesse 45.

de l'hydroxyle tertiaire. De telles réductions sont bien connues pour les cyclanols tertiaires[6] et même secondaires.[7]

Constantes du carotane (IV) (Entre parenthèses les valeurs indiquées par Sorm).

$$d_4^{20} = 0{,}8714\ (0{,}8704); \qquad n_D^{20} = 1{,}4739\ (1{,}4733);$$

$$RM_D \text{ obs} = 67{,}06; \qquad RM_D \text{ calc} = 67{,}10.$$

La comparaison des valeurs des constantes et des spectres I.R. de notre échantillon de carotane et de celui de Sorm et coll.[8] montre leur quasi-identité. Seules varient les intensités des bandes d'absorption. On trouvera dans[5] la comparaison graphique de ces spectres.

[6] G. Chiurdoglu, *Bull. Soc. Chim. Belg.* **44**, 527 (1935); *Ibid.* **50**, 31 (1941).
[7] H. E. Ungnade, *J. Org. Chem.* **12**, 361 (1947).
[8] J. Pliva, V. Herout, B. Sneider et F. Sorm, *Coll. Czech. Chem. Comm.* **18**, 500 (1953).

II. *Squelette du carotol. Hypothèse structurale*

1. *Déshydrogénation*

Plutôt que d'effectuer cette réaction sur charbon palladié, conditions favorables aux transpositions, nous avons choisi le sélénium comme agent de déshydrogénation. Ce dernier agit efficacement et rapidement déjà à 280°.

Il nous a paru, en outre, préférable de déshydrater au préalable le carotol dans des conditions douces. Traitant ce produit de déshydratation—le carotolène (VIII)—durant deux heures à 280°, par son poids de sélénium, nous avons obtenu un déshydrogénat dont nous avons séparé un produit azulénique avec un rendement de 6,3%. Il ne s'est pas formé de quantités décelables du naphtalénique isolé et identifié précédemment par Sorm et Urbanek.

2. *Azulénique* (V)

Le trinitrobenzénate* de cet azulénique purifié par cristallisation dans l'éthanol se présente sous forme d'aiguilles "violet-noir".

T.N.B. de (V); F = 148°–149°; $C_{21}H_{21}N_3O_6$

3. *Transposition*: *azulénique* V—*naphtalénique* VI

Nous n'avons pas observé de modification notable du rendement en azulénique en augmentant la durée de déshydrogénation: 6,3% pour deux heures, 7,1% pour quatre heures.

Par contre, lorsque cette durée est portée à neuf heures, le rendement tombe à 2%. De plus, la pureté de l'azulénique s'altère sensiblement. Des traces d'un autre, ou d'autres, azuléniques apparaissent au fur et à mesure que le traitement se prolonge, alors que nos expériences montrent qu'en même temps la concentration en naphtalénique de Sorm—1,7-diméthyl-4-isopropylnaphtalène (VI)—croît.

En effet, seul le déshydrogénat provenant d'un traitement d'une durée de neuf heures, fournit ce naphtalénique, par précipitation de son complexe trinitrobenzénique F = 132°–133°.

Ceci suggère que le naphtalénique (VI) *est le produit de transposition de l'azulénique* (V).

Tenant compte de la règle énoncée plus haut, nous pouvons formuler une hypothèse de travail selon laquelle le carotol posséderait une structure hydroazulénique.

Cette hypothèse a déjà, été avancée dans ce laboratoire par Vanderlinden.[5]

4. *Nature de l'azulénique* V. 1,7-*diméthyl*-4-*isopropylazulène*

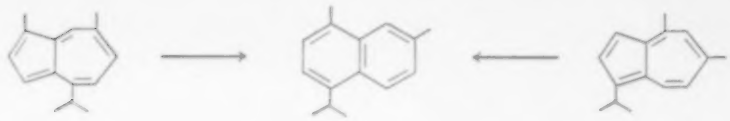
L'azulénique obtenu: T.N.B., F = 148°–149°, est différent de ceux déjà connus. Ceci est montré par les épreuves de mélange de T.N.B. de notre azulénique avec des échantillons authentiques de T.N.B. de S-guaiazulène, de T.N.B. de Se-guaiazulène et de T.N.B. de vétivazulène.

Tout ce que l'on sait de l'azulénique V, dérivant du carotol, est qu'il doit pouvoir fournir, par transposition rétropinacolique de Plattner,[9] le 1,7-diméthyl-4-isopropylnaphtalène.

Seuls deux azuléniques peuvent donner lieu à une telle transposition: le 1,7-diméthyl-4-isopropylazulène (V) et le 4,6-diméthyl-1-isopropylazulène (V′).

* Le complexe trinitrobenzénique sera désigné dorénavant par T.N.B.

[9] A. S. Pfau et Pl. A. Plattner, *Helv. Chim. Acta* **19**, 858 (1936).



V VI V'

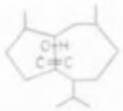
L'étude du spectre visible et l'application conjointe de la règle de Plattner[10] permettent le calcul de tels spectres pour V et V′ et, partant, le choix (Tableau 2), parmi ces deux structures, de celle appartenant à l'azulénique (V) du carotol. C'est le 1,7-diméthyl-4-isopropylazulène.

TABLEAU 2. COMPARAISON DES SPECTRES VISIBLES, CALCULES ET OBSERVES

Azulénique	Longueurs d'ondes (mμ)						
Azulène	699	667	632	667	578	557	535
Azulénique V du carotol (obs)	740	700	668	640	615	590	568
1,7-diméthyl-4-isopropylazulène (V) (spectre calculé)	735	703	668	643	614	593	571
4,6-diméthyl-1-isopropylazulène (V′) (spectre calculé)	705	673	638	613	584	563	541

5. *Conclusions*

Notre hypothèse de travail se précise: *le carotol serait un dérivé ènehydroxylique du* 3,10-*diméthyl*-6-*isopropylbicyclo*-(0,3,5)-*décane*.



Une telle structure—et ce qui suit a pour but d'en montrer la pertinence et d'en préciser les détails—serait d'un type nouveau dans la série des sesquiterpènes de la famille hydroazulénique.

III. *Emplacement du groupement hydroxyle dans le carotol*

1. *Examen du carotolène* (VIII) *et du dihydrocarotolène* (IX)

Dans leur étude, Sorm et Urbanek ont montré que la fonction alcoolique est tertiaire et liée au groupement isopropyle. Des deux positions possibles du groupement hydroxylique: au pied ou dans le creux de l'isopropyle, les auteurs ont choisi la deuxième, l'exocyclique.

Nous avons examiné les systèmes éthyléniques provenant de la déshydratation du carotol (I) et du dihydrocarotol (VII)

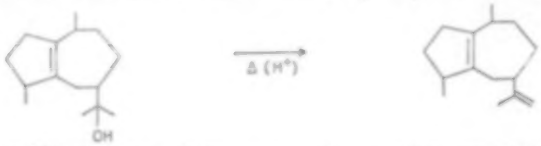
Dihydrocarotol (VII) $d_4^{20} = 0{,}9440$; $n_D^{20} = 1{\cdot}4856$; $[\alpha]_D^{20} = +3°.0$ (Sorm: $+3°1$); RM_D obs $= 68{,}15$; RM_D calc $= 68{,}59$.

[10] Pl. A. Plattner et E. Heilbronner, *Helv. Chim. Acta* **30**, 910 (1947); *Ibid.* **24**, 283E (1941).

Ces alcools ont été traités par une trace d'acide sulfurique et les oléfines correspondantes, carotolène (VIII) et dihydrocarotolène (IX), distillées, sous pression réduite, au fur et à mesure de leur formation.

Chiurdoglu et Van Walle[11] ont montré que, déshydratés de cette manière, les (1-hydroxy-1-méthyl-éthyl)-cyclanes fournissent soit exclusivement, soit en quantité prépondérante les isopropénylcyclanes correspondants.

Nous avons pu vérifier cette observation sur un cas plus proche du nôtre, celui du guaiol. Traité comme ci-dessous, celui-ci fournit presque exclusivement le guaiène.



Les oléfines VIII et IX, obtenues de la sorte, présentent les caractéristiques suivantes:
Carotolène (VIII) $Eb_2 = 83°–84°$; $d_4^{20} = 0{\cdot}8987$; $n_D^{20} = 1{\cdot}4993$; $[\alpha]_D^{20} = +20°{,}01$; RM_D obs = 66,12; RM_D calc = 66,13*
Dihydrocarotolène (IX) $C_{15}H_{26}$ $Eb_{0,8} = 58°–60°$; $d_4^{20} = 0{,}8776$; $n_D^{20} = 1{\cdot}4810$; RM_D obs = 66·83; RM_D calc = 66·60; $[\alpha]_D^{20} = -1°41 \pm 0{\cdot}56$ ($CHCl_3$; $c = 3{\cdot}335$).

Pas plus dans le spectre I.R. du carotolène que dans celui du dihydrocarotolène, on ne trouve, parmi les bandes d'absorption provenant des doubles liaisons, celles dues aux liaisons méthyléniques $>C{=}CH_2$: $\nu C{=}C$, 1640; $\delta(C{-}H)$, 890, 2δ, 1780 cm.$^{-1}$ L'absence de ces dernières traduit la position cyclique, au pied de l'isopropyle, du groupement hydroxyle. Cette conclusion est corroborée par l'observation faite en I.3, ayant trait à la facilité relative avec laquelle ce groupement s'hydrogénolyse au cours de la réduction catalytique du carotol.

2. *Ozonolyse du dihydrocarotolène* IX *dicétone* X

Un échantillon du dihydrocarotolène (IX), obtenu par traitement au bisulfate de potassium de VII, a été ozonolysé à $-60°$ dans l'éther de pétrole. Après avoir décomposé l'ozonide par du zinc en solution acétique, on obtient, avec un rendement de 30%, un dérivé $C_{15}H_{26}O_2$. Celui-ci est une dicétone car, d'une part, il ne réagit pas avec l'eau oxygénée et, d'autre part, il donne une bis-semicarbazone. Celle-ci est amorphe et fond entre 125° et 130°.
Dicétone X. $C_{15}H_{26}O_2$. $Eb_{0{\cdot}02} = 102°–105°$; $d_4^{20} = 0{\cdot}9724$; $n_D^{20} = 1{\cdot}4734$; RM_D obs = 69·29; RM_D calc = 6929;† $[\alpha]_D^{20} = -61°34 \pm 0{\cdot}75$ ($CHCl_3$; $c = 3{\cdot}065$).
La dicétone X fournit, par réduction, le diol XI correspondant.
Diol XI. $C_{15}H_{30}O_2$. $Eb_{0{\cdot}03} = 118°–120°$; $[\alpha]_D^{20} = -1°22 \pm 0{\cdot}80$ (C_2H_5OH; $c = 1{\cdot}630$).

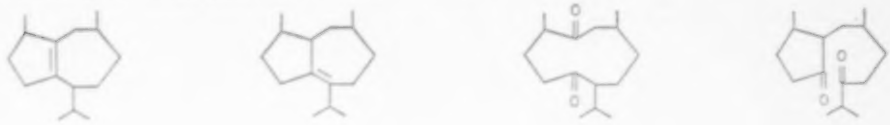
Le fait d'avoir obtenu une dicétone montre que la double liaison du

* RM_D obs: formule de Lorentz-Lorentz. RM_D calc: tables de réfractions atomiques de Eisenlohr.
† Compte-tenu de l'incrément de 0,55, valable pour les cycles C_8 à C_{13}.[12]

[11] G. Chiurdoglu et S. Van Walle, *Bull. Soc. Chim. Belg.* **66**, 612 (1957).
[12] A. L. Liberman, *Tables pour le calcul des réfractions moléculaires* Editions de l'Académie des Sciences S.S.S.R. (1948).

dihydrocarotolène (IX) est biquaternaire et endocyclique. Celle-ci n'est pas au pied d'un groupement méthyle, car X ne renferme pas de groupement acétyle (réaction haloforme négative).

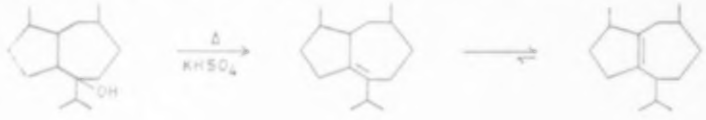
Seules deux positions: $\Delta^{1,7}$ et $\Delta^{6,7}$ de la double liaison doivent, dès lors, être retenues pour le dihydrocarotolène: IX et IX'.



IX IX' X X'

La structure IX' peut être rejetée, du fait que l'un des carbonyles de la dicétone X' correspondante devrait accuser une fréquence $\nu C{=}O = 1745\ cm^{-1}$ (cyclopentanone). Or, la dicétone préparée par nos soins présente les nombres d'ondes $\nu C{=}O$ suivants: 1701 et 1715 cm^{-1}.* Les structures du dihydrocarotolène et de la dicétone correspondantes sont, dès lors: IX et X.

Il s'ensuit que la déshydratation du dihydrocarotol (VIII) s'est accompagnée de la migration de la double liaison de la position $\Delta^{6,7}$ vers celle $\Delta^{1,7}$.



VIII IX' IX

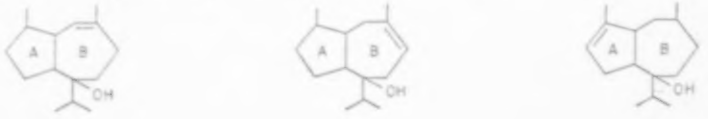
3. *Conclusions. Emplacement du groupement* OH *tertiaire dans le carotol*

L'absence dans le carotolène (VIII) et dans le dihydrocarotolène (IX), préparés d'après Van Volkenburgh, de chaînons $>C{=}CH_2$, méthylénique ou isopropylénique et l'obtention de la cycladione X permettent de conclure au caractère biquaternaire et endocyclique de la double liaison du IX et, partant, à la position cyclique, et au pied de l'isopropyle, du groupement OH dans le dihydrocarotol et, par conséquent, dans le carotol (I).

Dans les expériences ultérieures, nous verrons se confirmer cette conclusion.

IV. *Nature et position de la double liaison du carotol. Structure du cetodiol* XIII

La carotol présente deux bandes d'absorption $\delta(C{-}H)$ à 814 et à 824 cm^{-1}, ce qui traduirait le caractère quaternaire-tertiaire[14] de sa double liaison et signifierait que le carotol peut être représenté par l'une des trois structures ci-dessous:



I I' I''

* Le fait que la 1,5-cyclodécadione (X) présente deux fréquences distinctes, alors que la 1,6-cyclodécadione n'en possède qu'une seule (1717 cm^{-1})[13] s'expliquerait par la dissymétrie de la première ainsi que par la non-équivalence de ses carbonyles.

[13] G. Chiurdoglu, R. Fuks et B. Tursch, *Bull. Soc. Chim. Belg.* **67**, 191 (1958).

[14] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*. Methuen, London; John Wiley, New York (1958).

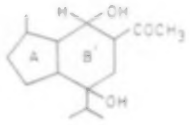
L'étude du cétodiol XIII devait nous permettre de déterminer la nature et l'emplacement de la double liaison* du carotol et, partant, le choix *pour ce dernier* de l'une des trois structures I, I', I".

1. *Cétodiol* XIII. *Détermination de sa structure*

Le carotol soumis à l'ozonolyse conduit à un solide cristallin XIII: F = 97°. On obtient, encore, ce même composé en traitant par du tétraacétate de plomb, ou bien par de l'acide periodique, le carotanetriol (III) (F = 142°), dérivé du carotol décrit en 1·2.

Cétodiol XIII: $C_{15}H_{26}O_3$. F = 97°.

Ce composé a déjà été obtenu et étudié par Sorm[1] qui lui avait attribué une formule de dicétone. En fait, c'est un cétodiol de structure XIII, c'est-à-dire le 3-acétyl-9-méthyl-5-isopropylbicyclo-(0,3,4)-nonan-2,5-diol, comme nous le montrons ci-après:

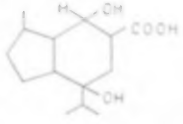


XIII

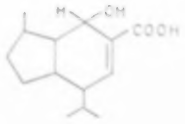
(a) *Le cétodiol* XIII *renferme un groupement acétyle.* Le composé XIII dont le spectre infra-rouge contient, en particulier, la fréquence $\nu C{=}O$ en 1701 cm^{-1}, conformément à la nature de son groupement carbonyle, oxydé par de l'hypoiodite de sodium fournit l'iodoforme et le dihydroxyacide cristallin XIV (le 3-carboxy-9-méthyl-5-isopropylbicyclo-(0,3,4)-nonan-2,5-diol) $C_{14}H_{24}O_4$. F = 163°; $[\alpha]_D^{20}$ = + 49°25 ± 1°12 (C_2H_5OH; c = 1·990).

Ce dernier forme facilement la lactone XV correspondante (voir en d).

Pyrolysé à 150°, le dihydroxyacide XIV perd une molécule d'eau et se transforme en l'hydroxyacide non saturé XVI (Δ^3-3 carboxy-9-méthyl-5-isopropylbicyclo-(0,3,4)-nonèn-2-ol). $C_{14}H_{22}O_3$. F = 131°.



XIV



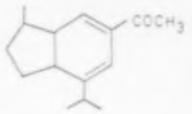
XVI

La conjugaison de la double liaison avec le groupement carboxylique se marque par l'accroissement de l'intensité de $\nu C{=}C$ et par l'abaissement de la fréquence de $\nu C{=}O$ à 1689 cm^{-1}.

(b) *Le cétodiol* XIII *renferme deux groupements hydroxyles, l'un secondaire, l'autre tertiaire. Diénone* XVIII. Traité par $KHSO_4$ à 180° le cétodiol XIII perd deux molécules d'eau pour donner la diénone XVIII (3-acétyl-9-méthyl-5-isopropylbicyclo-(0,3,4)-nona-2,4-diène).

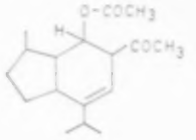
* Rappelons que pour Sorm et Urbanek cette double liaison est biquaternaire.

$C_{15}H_{24}O$. $Eb_{0.05} = 92°–93°$; $d_4^{20} = 0{\cdot}9750$; $n_4^{20} = 1{\cdot}5117$; RM_D obs = 66,98; RM_D calc = 66·15* $[\alpha]_D^{20} = -111°{\cdot}88 \pm 0{\cdot}97$ ($CHCl_3$; $c = 2{\cdot}610$).



XVII

D'autre part, le cétodiol XIII traité à reflux dans l'anhydride acétique, additionné d'une goutte de H_2SO_4, c'est-à-dire dans des conditions provoquant la déshydratation de la fonction OH tertiaire et l'acétylation du OH secondaire, fournit le cétoacétate non saturé XVII (Δ^3-2-acétoxy-3-acétyl-9-méthyl-5-isopropyl-bicyclo-(0,3,4)-nonène). $C_{17}H_{26}O_3$. $Eb_{0.05} = 110°–112°0$; $[\alpha]_D^{20} = +11°29$ ($CHCl_3$; $c = 2{\cdot}835$).



XVII

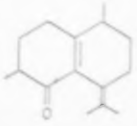
Le 3-acétyl-9-méthyl-5-isopropylbicyclo-(0,3,4)-nonan-2,5-diol (XIII) *renferme donc bien deux groupements alcooliques, l'un secondaire, l'autre tertiaire.*

(c) *Dans le cétodiol* XIII *le groupe* OH *secondaire est en β du groupement acétyle.* L'hydrolyse basique du cétoacétate non saturé XVII conduit non pas au cétoalcool attendu mais bien à la diénone XVIII correspondante: le 3-acétyl-9-méthyl-5-isopropylbicyclo-(0,3,4)-nona-2,4-diène. Ceci montre que le groupement OH secondaire du 3-acétyl-9-méthyl-5-isopropylbicyclo-(0,3,4)-nonan-2,5-diol XIII est en β du groupe acétyle. Plus précisément, il est en para du groupement isopropyle, comme il est montré dans le paragraphe d, ci-après.

(d) *Dans le cétodiol* XIII, *les groupements* OH sec., *acétyle et* OH tert. *occuppent respectivement les positions* 2,3,5. Lorsqu'on oxyde le cétodiol XIII, non pas comme en IV.1.a, par de l'hypoiodite de sodium, mais bien par de l'hypobromite, on observe la formation, aux côtés du dihydroxyacide XIV solide (le 3-carboxy-9-méthyl-5-isopropyl bicyclo-(0,3,4)-nonan-2,5-diol), de l'hydroxy-γ-lactone XV† correspondante: $\nu C{=}O = 1779\ cm^{-1}$.

Ceci fixe, dès lors, comme indiqué ci-dessus, en d, les positions des divers substituants

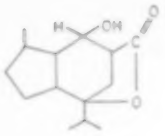
* L'exaltation observée est celle normalement relevée dans de tels cas. Elle est du même ordre, par exemple, que celle signalée pour le composé[15] Ci-dessous



† Ce type de lactone est assez fréquent. Citons deux exemples récents relatifs, l'un, à un dérivé sesquiterpénique,[15] l'autre, à un dérivé diterpénique.[16]

[15] K. Tsuda et K. Tanabe, *J. Amer. Chem. Soc.* **79**, 1009 (1957).
[16] J. Pudles, A. Diara et E. Lederer, *Bull. Soc. Chim.* 693 (1959).

du cycle B′ du cétodiol XIII et, partant, l'emplacement de la double liaison dans le carotol.



XV

2. *Nature et emplacement de la double liaison dans le carotol* (I)

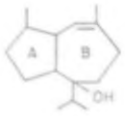
Cet emplacement ne peut être que $\Delta^{2,3}$ (structure I) et la double liaison* ne peut être que quaternaire-tertiaire, si l'on veut expliquer la formation, la nature et les diverses réactions du cétodiol XIII que nous venons d'étudier et dont on trouve un rappel succinct dans le schéma (Tableau 3) ci-après.

3. *Résumé—conclusions*

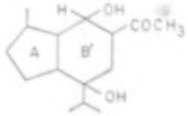
L'ensemble de réactions de cette première dégradation du carotol a permis de prouver la nature quaternaire-tertiaire de la double liaison, de fixer dans le cadre d'une structure hydroazulénique, son emplacement en $\Delta^{2,3}$ *en même temps que de déterminer, dans ce même cadre, la structure d'un produit important de dégradation du carotol, le cétodialcool* XIII.

V. *Détermination de la taille du cycle* B *du carotol*

En ce qui concerne la taille des cycles A et B du carotol (I), A se retrouve, tel quel, dans le cétodiol, tandis que B avant de s'y intégrer a procédé à l'expulsion d'un atome de carbone annulaire



I



XIII

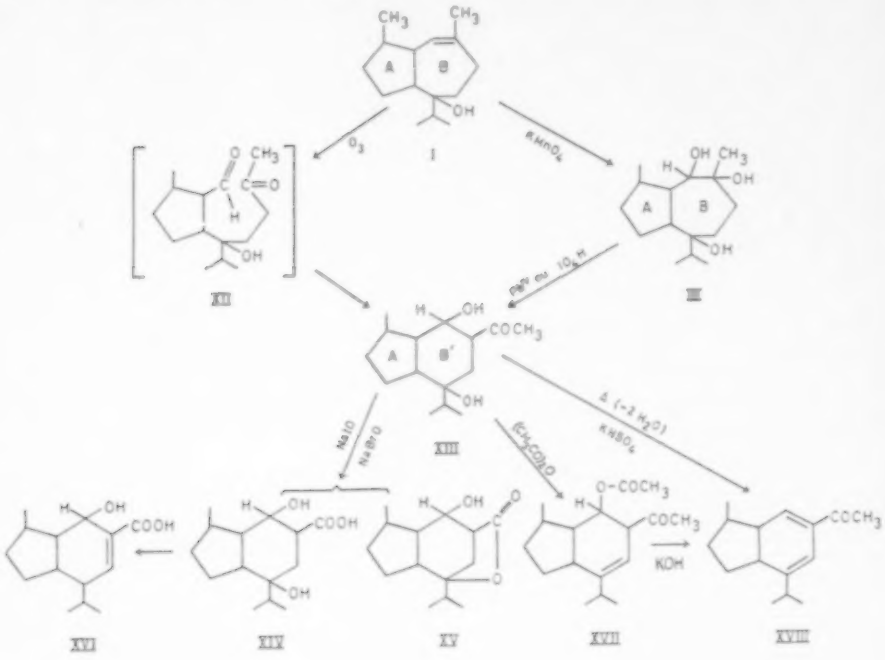
Ce dernier fait a été mis en évidence au paragraphe précédent. Il nous suffit, à présent, de montrer que le cycle B′ possède bien la taille hexacarbonée pour confirmer en même temps la taille heptacarbonée de l'anneau B et, partant, toute l'hypothèse structurale esquissée en II.5.

1. *Détermination de la taille du cycle* B *au niveau du cétoalcool* XIX

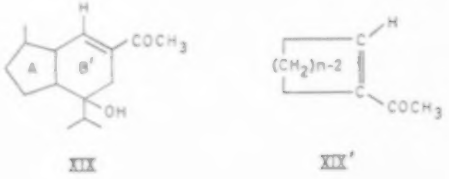
Un traitement basique, à chaud, détermine la déshydratation du cétodiol XIII en cétoalcool non saturé XIX (Δ^2-3-acétyl-9-méthyl-5-isopropylbicyclo-(0,3,4)-nonène-4-ol)

* Une position $\Delta^{3,4}$ de celle-ci (structure I′) aurait conduit à la δ-lactone ci-après, aisément identifiable par I.R. (νC=O entre 1735 et 1750 cm^{-1}).

TABLEAU 3. SCHEMA DE LA PREMIERE DEGRADATION DU CAROTOL (I). (Section IV.)



$C_{15}H_{24}O_2$. Eb. 0·05 = 107°; semicarbazone amorphe (F ~ 90°), malaisément purifiable $C_{16}H_{27}O_2N_3$



La molécule XIX possède une structure du type XIX'. De telles structures presentent dans l'U.V. une bande K forte dont la longueur d'onde maximum est liée à la taille du cycle:[17] 239 mμ pour $n = 5$; 232–233 mμ pour $n = 6$.

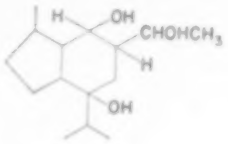
Le cétoalcool XIX examiné dans l'U.V. (spectre dans l'éthanol) présente une forte bande à 233 mμ ($\varepsilon = 10{\cdot}480$). On en conclut que dans XIX le groupement acétyle est fixé sur un cycle hexacarboné.

2. *Détermination de la taille du cycle* B′ *au niveau de la dihydroxycétone* XXII

Une deuxième détermination de la taille cyclique B′ a été effectuée sur l'oxadérivé XXII provenant du cétoalcool XIII, comme ci-après.

[17] W. M. Schubert et S. A. Sweeney, *J. Amer. Chem. Soc.* 77, 2297 (1955).

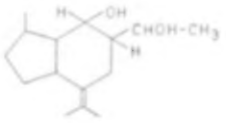
(a) *Triol* XX. La réduction au moyen de l'hydrure de lithium aluminium du cétodiol XIII fournit le triol XX: F = 108°–109°; $C_{15}H_{28}O_3$.



XX

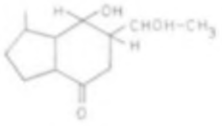
(b) *Diol éthylénique* XXI. La déshydratation formique du triol XX conduit au diol éthylénique XXI: F = 126°–127°. $C_{15}H_{26}O_2$.

Dans le spectre I.R. de ce diol éthylénique, on ne décèle pas de bande $\nu C{=}C$, ce qui est de règle pour ce type de double liaison biquaternaire.



XXI

(c) *Dihydroxycetone* XXII. L'ozonolyse dans l'acétone à −60° de l'éthylénique XXI fournit la dihydroxycétone XXII. $Eb_{0{\cdot}09} = 138°–140°$; $[\alpha]_D^{20} = +22{\cdot}08 \pm 1°36$; ($C_2H_5OH$; $c = 1{\cdot}630$).



XXII

La semicarbazone est un solide amorphe fondant de 115° à 120° et qui ne se laisse pas purifier, ce que reflète, par ailleurs, l'analyse élémentaire: calculé pour $C_{13}H_{23}O_2N_3$: C, 58·00%; H, 8·55%; N, 15·61%. Trouvé: C, 58·50; H, 8·29; N, 17·89. Cette analyse est toutefois susffiamment significative de la perte à l'ozonolyse de trois atomes de carbone, ceux du groupe isopropyle.

Le spectre I.R. de la dihydroxycétone XXII, relevé en solution dans CCl_4 (0,01 M/l), montre une seule bande carbonyle de fréquence de 1715 cm^{-1}.

Le cycle B′ *de la cyclanone* XXII *est donc bien hexacarboné.*

3. *Détermination de la taille du cycle* B′ *au niveau de la 9-méthyl-5-isopropylbicyclo-(0,3,4)-nonan-3-one* (XXVII)

Partant du cétodiol XIII, nous avons préparé la cyclanone XXVII, via les composés XVIII, XXIII, XXIV, XXV et XXVI (voir schéma du Tableau 5).

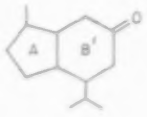
La déshydratation du cétodiol XIII, par $KHSO_4$ anhydre fournit la diénone XVIII déjà obtenue en IV.1.b. Sa réduction sur Ni-Ra, sous 80 atm de pression de H_2 et à 100°, conduit à l'alcool saturé XXIII ($Eb_{0\cdot05} = 90°–93°$). Celui-ci, oxydé à 20° par l'acide chromique en milieu acétique, donne la cétone XXIV: $Eb_{0\cdot05} = 80°–85°$; $d_4^{20} = 0\cdot9916$; $n_D^{20} = 1\cdot4917$; $[\alpha]_D^{20} = 6°90 \pm 0\cdot61$ ($CHCl_3$; $c = 3\cdot385$) $\nu C{=}O$: 1705 cm^{-1}.

On applique alors à cette méthylcycloalcoylcétone la réaction générale mise au point par Emmans et Lucas.[18] La cétone XXIV est transformée en acétate XXV, par action de l'eau oxygénée à 100% et de l'anhydride trifluoracétique, dans le chlorure de méthylène. L'acétate XXV formé est une huile. Il présente les deux pics caractéristiques des acétates:

$$\nu C{=}O: \ 1735 \ cm^{-1} \quad \text{et} \quad \nu C{=}O: \ 1250 \ cm^{-1}$$

L'hydrolyse de l'acétate XXV par la potasse alcoolique conduit à l'alcool XXVI correspondant.

On s'assure que le spectre de celui-ci ne renferme aucune bande $\nu C{=}O$, puis l'oxyde par CrO_3 en la cétone XXVII correspondante, la 9-méthyl-5-isopropylbicyclo-(0,3,4)-nonan-3-one.

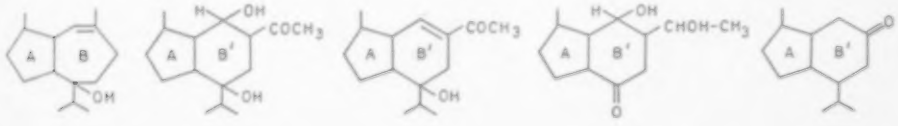


XXVII

Cette cétone, dont on vérifie, par ailleurs, le caractère saturé (test à l'eau de brome très diluée), présente dans l'infra-rouge une bande $\nu C{=}O$ à 1713 cm^{-1} (sol.: CCl_4 0·01 M/l). *La taille du cycle* B' *est, par conséquent, hexaméthylénique.*

4. *Conclusions*

Il a été montré par l'étude des trois produits de dégradation suivants (XIX, XXII, XXVII) *que la taille de leur cycle* B' *est indiscutablement hexacarbonée. Il en est de même du cétodialcool* (XIII) *dont dérivent ces produits par les voies schématisées dans le Tableau* 4.

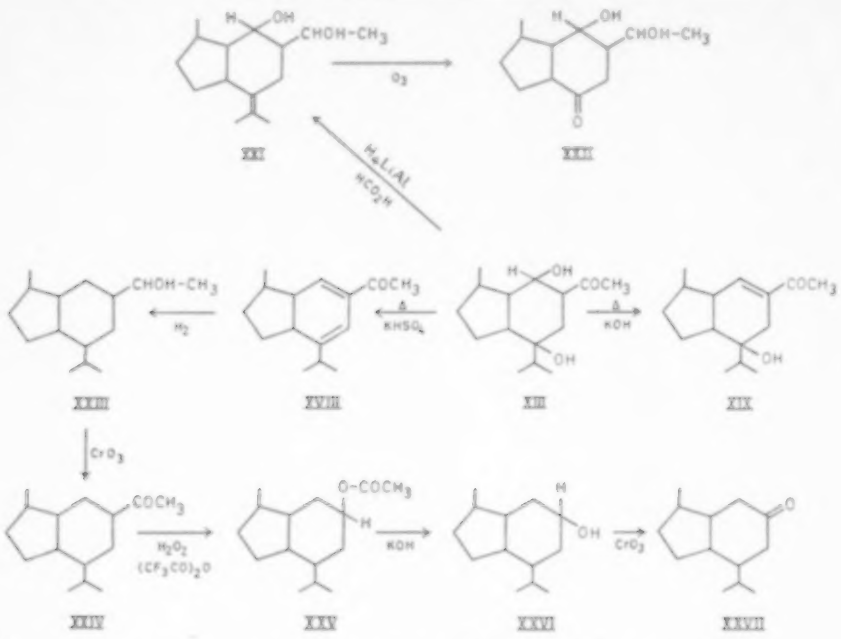


I XIII XIX XXII XXVII

Dès lors, la taille du cycle B *du carotol* (I) *est bien heptacarbonée comme le laissait supposer notre hypothèse de travail.*

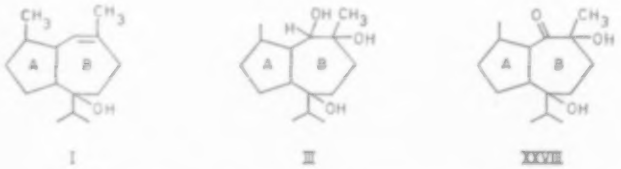
[18] W. D. Emmans et G. B. Lucas, *J. Amer. Chem. Soc.* 77, 2287 (1955).

TABLEAU 4. SCHEMA DE LA DEUXIEME DEGRADATION DU CAROTOL. (Section V.)



VI. *Détermination directe de la taille du cycle* B *du carotol*

Il nous a paru intéressant d'effectuer une détermination directe de la taille de l'anneau heptanique du carotol. Pour ce faire, la meilleure voie à suivre était assurément de partir du carotanetriol (III) F = 142°, produit aisément accessible, et de le transformer, au moyen de l'acide chromique, en l'hydroxycétone correspondante XXVIII. Il était ensuite aisé d'en relever la taille cyclique par une simple mesure de la fréquence $\nu C{=}O$.



I II XXVIII

On sait, en effet, que dans de tels cas cette fréquence n'est pas affectée par la présence en α d'un groupement OH axial.[19,20] Seule, une position équatoriale de OH exerce un léger abaissement par le truchement du lien H.[20] Ainsi:

[19] J. C. Schehan, R. C. O'Neill et M. A. Withe, *J. Amer. Chem. Soc.* **72**, 3376 (1950).
[20] A. R. H. Cole and G. T. A. Muller, *J. Chem. Soc.* 1224 (1959).

Dans notre cas (XXVIII), nous nous attendions à relever une fréquence $\nu C{=}O$ à 1702 cm^{-1}. L'oxydation chromique a été pratiquée en solution acétique selon les règles prescrites: solution à 5%, température de réaction: 20°, durée de la réaction: 24 hr. Elle a conduit à un produit liquide dont la bande d'absorption $\nu C{=}O$ est à 1712 cm^{-1}, mais comporte un épaulement à 1701 cm^{-1}.

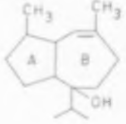
Dans une deuxième expérience,* l'addition de la solution acétique de CrO_3 a été extrêmement lente (20 ml en 60 min) et la température de la réaction abaissée à 15°. On a séparé, avec un bon rendement, un produit dont le spectre (sol. 0,02 M/l dans CCl_4) renferme une bande très fine de $\nu C{=}O$ à 1701 cm^{-1}, avec un léger épaulement à 1712 cm^{-1}. L'explication de cet étrange comportement de notre 1,2-diol serait la suivante.[21] En solution acétique d'acide chromique, deux réactions compétitives entrent en jeu. La première concerne l'oxydation de l'hydroxyle secondaire et l'apparition de l'α-hydroxycétone désirée. La seconde provoque la rupture du lien C_1—C_2, comme le fait le tétraacétate de plomb.

Dans nos expériences, en même temps que nous formions l'α-hydroxycétone ($\nu C{=}O$: 1701 cm^{-1}) apparaissait un pourcentage élevé (première expérience) ou faible (deuxième expérience) du produit de scission ($\nu C{=}O$: 1712 cm^{-1}). Pratiquée en solution acétique, l'oxydation chromique apparaît comme un moyen délicat et qui est à proscrire. Il conviendrait de la pratiquer en solution pyridinique.

Ce problème a retenu toute notre attention et est traité actuellement dans le cadre plus vaste d'une étude du carotol, dont le présent travail constitue la *première* partie.

VII. *Conclusions*

Il est montré dans le présent travail que le carotol possède non pas la structure décalanique de Sorm et Urbanek, mais bien une structure azulénique d'un type nouveau et qui n'obéit pas à la règle biogénétique de Ruzicka. Le carotol est le Δ²,³-3,10-*dimethyl-6-isopropylbicyclo-(0,3,5)-décan-6-ol.*



I

De nombreux dérivés du carotol ont été obtenus, dans la plupart des cas pour la première fois, et leur structure déterminée.

PARTIE EXPERIMENTALE

A. *Séparation du carotol* (I) *et du daucol* (II)

1. *Carotol*

L'huile de *Daucus Carota*† (950 g), préalablement neutralisée, a subi quatre tours de distillation fractionnée, les deux derniers au moyen d'une colonne Todd de 20 plateaux théoriques. Carotol (I) (obtenu 230 g). $Eb_{0\cdot2} = 97°$; $d_4^{20} = 0{\cdot}9653$; $n_D^{20} = 1{\cdot}4982$; $[\alpha]_D^{20} = +21°13$.

* Celle-ci a été pratiquée par M. R. Smolders, *Dissertation* U.L.B., en cours.

† L'huile de *Daucus Carota* nécessaire à ce travail nous a été gracieusement fournie par la N.V. Chemische Fabriek Naarden de Hollande. Il nous est agréable de remercier le Directeur de cette firme ainsi que le Docteur R. M. Ruys, son Directeur scientifique.

[21] W. A. Waters, *Quart. Rev.* **12**, 277 (1958).

Purification du carotol par chromatographie. 50 g de carotol obtenu en A.1 sont chromatographiés sur 4 kg de silice d'activité I–II. Eluant: éther de pétrole + 1% de benzène. Quatre tours de chromatographie conduisent à 10 g de carotol dont les constantes sont indiquées dans le Tableau 1.

(Analyse. Calculé pour $C_{15}H_{26}O$: C, 81·04; H, 11·73. Trouvé: C, 80·84; H, 11·83%).

2. *Daucol* (II)

Dans les résidus de distillation de l'huile, précipite le daucol (II), 5 g, que l'on recristallise dans l'éther de pétrole (Eb = 30°–70°). Daucol: F = 118°.

(Analyse. Calculé pour $C_{15}H_{26}O_2$: C, 75·47; H, 10·97. Trouvé: C, 75·48; H, 10·97%).

3. *Préparation du carotanetriol* (III)[4]

Cette préparation a été faite en suivant le mode opératoire décrit par Sorm et Urbanek.[4] 10 g de carotol (I) ont fourni 5 g (Rd = 44%) de carotanetriol recristallisé: F = 142°.

(Analyse. Calculé pour $C_{15}H_{28}O_3$: C, 70·28; H, 10·97. Trouvé: C, 70·10; H, 11·00%).

4. *Carotane* (IV)

414 mg (0·00199 M) de carotol dissous dans 4 ml d'acide acétique glacial sont hydrogénés en présence de noir de platine. On suit la technique indiquée par.[6] Quantité d'hydrogène absorbé en 12 hr sous 775 mm Hg et à 17°, 91·0 ml. Calculé: 92·50 ml. Le carotane (IV) est chromatographié sur gel de silice.

(Rapport 1/100; éluant: éther de pétrole, fractions de 50 ml: Fr 1 = 0·22 g; Fr 2 = 0·06 g; Fr 3 = 0·07 g; Fr 4 = 0·069 g). La première fraction consiste en carotane pur.

B. *Préparation du carotolène* (VIII)[4]

1. *Déshydratation du carotol par l'acide formique*

Opérant d'après (4) on obtient à partir de 5 g (0·0025 M) de carotol 3·5 g (0·0171 M) d'oléfine soit 76% Rd. $Eb._2$ = 84°–85°; d_4^{20} = 0·9002; n_D^{20} = 1·4980.

2. *Déshydratation du carotol par le bisulfate de potassium*

20 g (0·09 M) de carotol sont chauffés durant 30 min, à 100°, en présence de 10 g de bisulfate de potassium. L'oléfine formée est extraite à l'éther, chromatographiée sur du gel de silice. On obtient ainsi 16 g de carotolène (VIII). Rd = 87%.

3. *Déshydratation du carotol d'après la méthode de van Volkenburgh*[22]

10 g (0·045 M) de carotol additionnés de 1 goutte de H_2SO_4 concentré sont placés dans un ballon connecté à un appareil de distillation à trois éléments de Vigreux. On chauffe à 150°, sous 0·5 mm Hg, de manière à ne distiller que l'éthylénique humide (82°). On isole ainsi 8·2 g (0·04 M) de carotolène. Rendement 90%. Constantes: III.1.

C. *Déshydrogénation*

1. *Déshydrogénation du carotolène* (VIII) *durant 2 heures*

(a) *Mode opératoire.* 16 g (0·078 M) du carotolène préparé comme en B.2 sont traités, durant 2 hr à 280°, par 16 g de sélénium. Le mélange réactionnel bleu est repris par 100 ml d'éther de pétrole (Eb: 30°–70°) et la solution agitée pendant 2 hr avec 100 ml d'acide phosphorique concentré.

(b) *Azulénique* (V). La couche acide est lavée à l'éther de pétrole puis on décompose le complexe phosphorique par l'eau glacée. L'azulénique libéré est extrait à l'éther de pétrole et la solution est neutralisée puis séchée. Le solvant chassé, on obtient 1 g d'une huile bleue (6,3% Rd) T.N.B.: F = 148°–149° après plusieurs cristallisations dans l'éthanol.

(Analyse. Calculé pour $C_{21}H_{21}N_2O_6$: C, 61·31; H, 5·11; N, 10·44. Trouvé: C, 60·50; H, 5·02; N, 10·44).

Epreuve de mélange avec T.N.B. de S-guaiazulène (F = 149°) abaissement d'environ 20°.

Epreuve de mélange avec T.N.B. de Sc-guaiazulène (F = 153°) abaissement d'environ 20°.

Epreuve de mélange avec T.N.B. de vétivazulène (F = 150°) abaissement d'environ 20°.

[22] R. van Volkenburgh, K. W. Greenlee, J. M. Derfer et C. E. Boord, *J. Amer. Chem. Soc.* **71**, 172 (1949).

(c) *Naphtalénique.* La fraction restant après l'extraction à l'acide phosphorique est neutralisée. On sépare 43·2 g d'huile. Celle-ci est chromatographiée sur gel de silice. Les différentes fractions obtenues sont traitées au trinitrobenzène. Aucune ne fournit de précipité de T.N.B.

2. *Déshydrogénation du carotolène durant 4 heures*

Mode opératoire et résultats identiques à ceux obtenus en C.1.

3. *Déshydrogénation du carotolène* VIII *durant 6 heures*

Mode opératoire identique à celui décrit en C.1. On isole un azulénique de pureté altérée dont on sépare le produit de T.N.B.: F = 148°–149°. Il n'a pas été isolé d'aromatique.

4. *Déshydrogénation durant 9 heures*

Mode opératoire décrit en C.1. On obtient 0,4 g d'azulénique, T.N.B.: F = 90°, après deux recristallisations dans l'éthanol.

5. *Naphtalénique* (VI)

Dans l'essai C.4, opérant en fin de l'opération comme en C.1.c, on a décelé dans les fractions de tête de la chromatographie, le naphtalénique de Sorm (VI): T.N.B.: F = 132°–133°. On a séparé 100 mg de T.N.B. correspondant à 25 mg de 1,7-diméthyl-4-isopropylnaphtalène. Signalons que ni le picrate ni le styphnate n'ont pu être formés par traitement adéquat de la partie aliquote de la fraction naphtalénique.

D. *Première dégradation du carotol*

1. *Dihydrocarotol* (IX)

Un premier échantillon a été obtenu par hydrogénation du carotol (25 g) sur Ni-Ra dans l'éthanol, sous 100 atmosphères de pression. Rendement 87%. Un autre échantillon de dihydrocarotol a été préparé par hydrogénation du carotol (25 g) sur noir de platine, sous pression atmosphérique.

2. *Dihydrocarotolène* (IX)

Mode opératoire comme en B.1. Constantes: III.1.

3. *Ozonolyse du dihydrocarotolène en la dicétone* X

On opère exactement comme en C.1. et on obtient à partir de 20 g de dihydrocarotol, 12 g d'une huile que l'on percole sur silice puis distille sous pression réduite. On obtient 7,1 g (0·03 M) de dicétone X (Rd = 30%). Il s'est formé, en outre, 3 g d'une fraction acide. Celle-ci n'a pas été étudiée. Dicétone X. (Analyse. Calculé pour $C_{15}H_{26}O_2$: C, 57·95; H, 9·10. Trouvé: C, 57·84; H, 9·09%).

4. *Traitement de la dicétone* X *par* H_2O_2 *en milieu basique*[22]

Traitant d'après[22] 5 g de dicétone X on a récupéré pratiquement l'entièreté du produit de départ.

5. *Réaction haloforme au départ de la dicétone* X

A 2 g (0·0084 M) de X dissous dans 30 ml de dioxane additionnés de 15 ml de NaOH aq (sol 10%), on ajoute, en agitant en-dessous de 30°, une solution aqueuse formée de 20 g KI, 10 g I_2, 100 ml H_2O jusqu'à coloration permanente. On chauffe 2 min à 60°, détruit l'excès de I_2 (NaOH). Il n'y a pas formation d'iodoforme, ni d'autre précipité.

Fractions obtenues: neutre (1·85 g), produit inchangé et acide: 0·15 g.

6. *Oxydation de dicétone* X *par de l'hypobromite de sodium*

10 g de X (0·042 M) sont agités durant 24 hr à la température du laboratoire avec une solution contenant : 100 ml H_2O, 60 g NaOH, 70 g Br_2. Après de laps de temps, on détruit l'excès d'hypobromite (SO_2) et extrait le neutre de l'oxydation à l'éther. Résidu de l'extraction: huile, 4 g. La solution aqueuse est acidulée puis extraite à l'éther. Résidu acide: 5 g (Rd 50%).

[22] P. Nafa et G. Ourisson, *Bull. Soc. Chim.* 1115 (1954).

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7. *Réduction de la dicétone* X *en diol* XI *par de l'hydrure de lithium aluminium*

5 g (0·0021 M) de X dans 100 ml d'éther anhydre sont traités, goutte à goutte, par une suspension agitée énergiquement, de 2 g de H_4LiAl dans 400 ml d'éther. On chauffe 12 hr à reflux, puis décompose par 5 ml d'éthanol. Le mélange est versé, par petites portions, dans 100 ml de H_2SO_4 à 10% maintenu à 0°. La solution éthérée est décantée, séchée, l'éther est chassé et le résidu distillé. On obtient ainsi 4·4 g (86% de Rd.) de diol XI.

Diol XI. (Analyse. Calculé pour $C_{15}H_{30}O_2$: C, 74·29; H, 12·30. Trouvé: C, 74·70; H, 12·30%).

E. *Cétodiol* (XIII)

1. *Préparation du cétodiol par ozonolyse du carotol*

15 g (0·0675 M) de carotol (I) sont dissous dans 80 ml d'éther de pétrole (Eb = 30°–70°) et l'on fait passer à −70° un courant d'oxygène ozonisé à 0,03%. L'ozonide précipite sous forme d'un solide blanc. Celui-ci est décanté, puis dissous dans 100 ml d'acide acétique pur glacial. On ajoute, alors, de l'eau glacée goutte à goutte, jusqu'à début de trouble, puis décompose l'ozonide par 20 g de Zn, introduit par petites portions, en refroidissant de manière à maintenir la température en-dessous de 30°. On reprend par l'eau et extrait à l'éther. L'extrait éthéré est neutralisé par une solution à 10% de bicarbonate de sodium, lavé à l'eau et, enfin, séché. Le solvant chassé, le résidu neutre est cristallisé dans un mélange de benzène et d'éther de pétrole. F: 97°. Rendement: 8·5 g (0·0355 M) soit 50%.

(Analyse. Calculé pour $C_{15}H_{28}O_3$: C, 70·86; H, 10·23. Trouvé: C, 69·73; H, 10·10%).

2. *Préparation du cétodiol* XII *via carotanetriol* (III)

(a) *Préparation du carotanetriol* (III). Voir A.3.

(b) *Oxydation du carotanetriol* (III) *en le cétodiol* XIII (α)-*Oxydation du carotanetriol par du tétraacétate de plomb.* 1 g (0·039 M) de carotanetriol (III) F = 142° est dissous dans 10 ml d'acide acétique glacial. On ajoute goutte à goutte une solution de 2·5 g de tétraacétate de plomb dans 10 ml d'acide acétique. L'agitation est vigoureuse et la température est maintenue entre 40° et 50°. Après 30 min, le mélange est versé dans l'eau glacée et extrait à l'éther. On lave, puis sèche l'extrait dont le résidu (0·75 g), une huile, est cristallisé dans un mélange 1/3 de benzène et d'éther de pétrole. La recristallisation livre finalement 0·40 g (0·00158 M) de XIII (Rd. 40%) F = 94°–95°.

(β)-*Oxydation du carotanetriol* (III) *par l'acide periodique*[4]

1 g de III traité d'après le mode opératoire[4] fournit, avec 30% de rendement, le cétodiol (XIII) F = 95°–96°.

3. *Identité des échantillons* 1, 2.α et 2.β *de cétodialcool* XIII

Une triple épreuve de mélange montre l'identité de ces trois échantillons.

F. *Deuxième dégradation du carotol*

1. *Oxydation haloforme du cétodiol* XIII *en dihydroxyacide* XIV

On oxyde 3 g de cétodiol XIII par de l'hypoiodite de sodium, en procédant comme en E.5.

On filtre l'iodoforme formé (F = 120°), extrait à l'éther (pas de neutres), acidule et extrait à nouveau l'éther. La fraction acide (2·7 g) est cristallisée dans un mélange de benzène et d'éther de pétrole. On obtient 1·05 g (0·0014 M) de dihydroxyacide cristallin XIV F = 163°. Rendement: 35%. (Analyse. Calculé pour $C_{14}H_{28}O_4$: C, 65·62; H, 9·37. Trouvé: C, 65·40; H, 9·43%).

2. *Déshydratation pyrolitique du dihydroxyacide* (XIV) *en l'hydroxyacide* XVI

1 g d'acide XIV (F = 163°) est chauffé à 250° sous une pression de 0·05 mm de Hg. Il distille une huile qui ne tarde pas à cristalliser. Le solide est purifié par recristallisation dans un mélange de benzène et d'éther de pétrole. On isole, finalement, 160 mg (0·00017 M) d'acide XVI (Rd. 20%) F = 131°. (Analyse. Calculé pour $C_{14}H_{22}O_3$: C, 70·39; H, 9·20. Trouvé: C, 69·85; H, 9·19%).

3. *Déshydratation bisulfatique du cétodiol* XIII *en la diénone* XVIII

8·2 g (0·032 M) de cétodiol XIII sont traités durant 30 min à 160°, sous une pression de 100 mm de Hg, par 10 g de $KHSO_4$. On extrait à l'éther, lave et sèche la solution éthérée, chasse le solvant

et sépare, par distillation sous pression réduite, 2·7 g [(0·0124 M), Rd 38%] de cétone XVIII. (Analyse. Calculé pour $C_{15}H_{24}O$: C, 82·56; H, 10·09. Trouvé: C, 82·27; H, 10·10%).

4. *Acétylation du cétodiol* XIII *en cétoacétate non saturé* XVII

On mélange 12 g (0·048 M) de cétodiol XIII avec 36 ml d'anhydride acétique, on ajoute 1 ml de H_2SO_4 anh. puis on chauffe deux hr, à reflux. Après les traitements d'usage, on isole 5·4 g (0·019 M) de cétoacétate non saturé XVII: $Eb._{0·05}$ = 110°–112°. Rendement 40%. (Analyse. Calculé pour $C_{17}H_{26}O_3$: C, 73·38; H, 9·35. Trouvé: C, 73·41; H, 9·31%).

5. *Hydrolyse du cétoacétate* XVIII *en la diénone* XVIII

4·9 g (0·0179 M) de cétoacétate XVIII dissous dans 20 ml de NaOH alcoolique à 10% sont chauffés 2 hr à reflux. Le mélange est versé dans l'eau et l'on extrait à l'éther la diénone XVIII ($Eb._{0·04}$ = 88°–91°): 3 g (0·014 M) soit 78% de rendement. La diénone XVIII a déjà été obtenue en F.4.

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G. *Troisième dégradation*

1. *Déshydratation du cétodiol* XIII *en cétoalcool non saturé* XIX

3 g (0·0118 M) de XIII sont chauffés à reflux avec 20 ml de KOH alcoolique à 10%. On dilue à l'eau, extrait à l'éther. Le résidu (1 g, soit 35% de rendement) bout, sous 0·05 mm Hg, à 107°. Semicarbazone amorphe, difficilement purifiable (F ~ 90°).

(Analyse. Calculé pour $C_{16}H_{27}O_2N_3$: C, 65·52; H, 9·21. Trouvé: C, 65·58; H, 9·37%).

2. *Réduction par* H_4LiAl *du cétodiol* XIII *en triol* XX

On traite, comme en D.7, 3 g (0·0118 M) de cétodiol XIII par 3 g de H_4LiAl. Le produit de la réduction recristallisé dans un mélange 1/3 de benzène–éther de pétrole, fond à 108°–109°. Rendement 2 g (0·008 M) soit 68%.

(Analyse. Calculé pour $C_{15}H_{28}O_3$: C, 70·30; H, 10·92. Trouvé: C, 70·35; H, 10·70%).

3. *Déshydratation du triol* XX *en diol non saturé* XXI

9·3 g (0·036 M) de triol sont déshydratés par l'acide formique, suivant le mode opératoire décrit en B.1. Le produit de la réaction, recristallisé dans un mélange 1/3 de benzène-éther de pétrole, fond à 126°–127°. Rendement: 7·5 g (0·0315 M) soit 88%.

(Analyse. Calculé pour $C_{15}H_{26}O_2$: C, 75·63; H, 10·90. Trouvé: C, 75·60; H, 10·87%).

4. *Ozonolyse du diol non saturé* XXI *en dihydrocétone* XXII

7 g (0·03 M) de diol XXI, F = 126°–127°, dissous dans 50 ml d'acétone, sont ozonolysés à −70°, selon le mode opératoire décrit en D.1.

La fraction neutre—la dihydroxycétone XXII—a été isolée avec 69% de rendement (4·4 g soit 0·0207 M). C'est une huile, $Eb._{0·09}$ = 135°–140°, dont la semicarbazone est amorphe, impurifiable: F ~ 115°–120°.

(Analyse. Calculé pour $C_{13}H_{23}O_3N_3$: C, 58·00; H, 8·55; N, 15·61. Trouvé: C, 58·50; H, 8·29; N, 17·98%). La fraction acide (0·6 g) de l'ozonolyse n'a pas été examinée.

5. *Réduction de la cétone* XVIII *en l'alcool saturé* XXIII

7 g (0·032 M) sont hydrogénés sur Ni-Ra en solution alcoolique, à 80°, sous 100 atmosphères de pression. Rendement: 7 g (0·031 M) soit 96%.

6. *Oxydation chromique de l'alcool* XXIII *en la cétone* XXIV

12·3 g (0·055 M) d'alcool sont dissous dans 50 ml d'acide acétique glacial. On ajoute, par petites portions et en agitant, 8·5 g d'acide chromique dissous dans 100 ml d'acide acétique. La température ne peut excéder 20°. On laisse reposer 12 hr à la température ordinaire. L'excès d'acide chromique est détruit au méthanol. On dilue à l'eau, extrait à l'éther, neutralise, lave et sèche la solution éthérée. L'éther évaporé, le résidu est distillé ($Eb._{0·09}$ = 85°). Rendement 6·6 g (0·03 M), soit 56%.

7. *Oxydation par le perhydrol, de la cétone* XXIV *en l'acétate* XXV

Une solution contenant 9·9 ml d'anhydride trifluoroacétique, 14·5 ml de chlorure de méthylène, 1·5 ml de perhydrol à ~100% est ajoutée, goutte à goutte, sous agitation, à un mélange formé de

6·5 g de cétone XXIV, de 20·3 g de phosphate acide de Na et de 29 g de chlorure de méthylène. On chauffe à reflux durant 1 hr.

Les sels formés sont filtrés et lavés au chlorure de méthylène; les filtrats combinés sont lavés avec une solution de $NaHCO_3$ à 10%, à l'eau puis séchés. On chasse le gros du solvant, ajoute 21 ml de méthanol, 3 ml d'acide acétique, 5·6 g de réactif de Girard. On chauffe 12 hr à reflux. Le mélange est versé sur 90 ml d'eau, la température étant maintenue à 0°. On neutralise partiellement par une solution de 3·8 g de $NaHCO_3$ dans 15 ml de H_2O. La solution est extraite au chlorure de méthylène. L'extrait est lavé par une solution diluée de bicarbonate de sodium, à l'eau, puis séchée.

Après évaporation du solvant on isole 3·3 g d'acétate XXV. Le rendement est de 47·5%.

8. *Hydrolyse de l'acétate* XXV *en l'alcool* XXVI

3·3 g (0·0138 M) d'acétate dissous dans 40 ml de KOH alcoolique à 10% sont chauffés 2 hr à reflux. On obtient finalement 2·4 g (0·0123 M) d'alcool, soit un rendement de 89%.

9. *Oxydation chromique de l'alcool* XXVI *en la cétone* XXVII

On met en oeuvre 2·4 g d'alcool dissous dans 15 ml d'acide acétique. Cette solution est traitée par une autre solution contenant 3 g de CrO_3, 30 ml d'acide acétique et 1 goutte de H_2SO_4. Le mélange est laissé au repos 50 hr à 20°. Pour le reste, on se reportera au G.6.

On obtient 1·5 g de cétone XXVII, dont on prépare la semicarbazone. Un test à l'eau de brome diluée montre que la cétone XXVII est saturée. On en relève le spectre infra-rouge en solution dans CCl_4 (0·02 M/l).

H. *Oxydation du carotanetriol* III *par l'acide chromique en solution acétique*

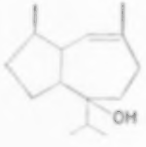
1. *Premier essai*

On dissout 1 g de triol dans 10 ml d'acide acétique glacial. Sous agitation et à 20°, on ajoute une solution de 1 g d'acide chromique dans 15 ml d'acide acétique glacial. Après un repos de 24 hr à 20°, on dilue à l'eau et extrait à l'éther. La solution éthérée est neutralisée, lavée et séchée. On évapore le solvant et obtient un résidu huileux que l'on distille: 0·4 g (rendement 40%). On en mesure l'absorption dans la région de 1600–1800 cm^{-1} (solution dans CCl_4, 0·02 M/l). Bande forte de νC=O à 1712 cm^{-1}, avec un épaulement à 1701 cm^{-1}.

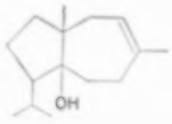
2. *Deuxième essai*

On opère comme en H.1 mais l'addition de l'oxydant prend 60 min et la température de l'expérience est fixée à 15°. Bande forte et fine de carbonyle: νC=O à 1701 cm^{-1}, avec épaulement à 1712 cm^{-1}.

Note ajoutée pendant la correction des épreuves. Dans une note à l'éditeur* du 27 juillet dernier nous avons indiqué la structure du carotol (1) telle qu'elle résulte du présent travail. Dans une autre note à l'éditeur,† parue le 21 septembre, F. Sorm *et al.* attribuent, de leur côté, au carotol, la structure (2).



1



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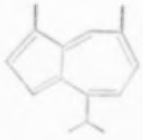

3

Toutes les expériences signalées dans les deux travaux s'expliquent aussi bien par l'une ou l'autre de ces deux structures (1) et (2), à l'exception de la déshydrogénation dont le résultat ne saurait être interprété par la formule (2). Or, le spectre visible de l'azulénique obtenu par la déshydrogénation du carotol n'est compatible (règle de PLATTNER) qu'avec le seul dérivé 1,4,7-trialcoylé (3).

* G. Chiurdoglu et M. Descamps, *Chem. & Ind.* 1377 (1959).
† V. Sykora, L. Novotny et F. Sorm, *Tetrahedron Letters* No. 14, 24 (1959).

Tetrahedron, 1960, Vol. 8, pp. 291 to 292. Pergamon Press Ltd. Printed in Northern Ireland

SYNTHESIS OF CALYCANINE

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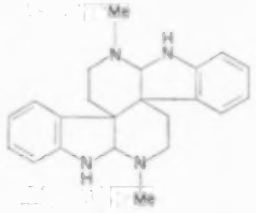
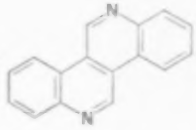
Abstract—Calycanine, the degradation product of the alkaloid calycanthine, has been synthesized.

THE alkaloid calycanthine isolated from various species of calycanthaceae has been assigned[1] structure (I). Dehydrogenation of calycanthine yields[2] a base, calycanine, $C_{16}H_{10}N_2$, formulated[1] as quinolino(4′:3′-3:4)quinoline (II). This structure has been reported[3] to have been confirmed by a synthesis from isoindigo by Clark and Woodward, but details have not been published. A new independent synthesis of calycanine has been devised and is reported here.



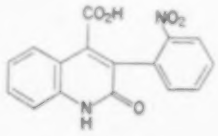
I



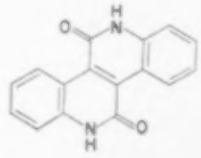
II

Aeschlimann[4] has condensed isatin with phenylacetyl chloride; the N-phenylacetyl isatin obtained underwent rearrangement in alkali to 3-phenyl-2-quinolone-4-carboxylic acid.

Isatin was condensed with *o*-nitrophenylacetyl chloride, but the N-acyl derivative could not be obtained pure. The crude product on treatment with alkali and subsequent acidification yielded 3-*o*-nitro-phenyl-2-quinolone-4-carboxylic acid (III), with infra-red bands at 5·95 (COOH) and 6·1 μ (amide). Catalytic hydrogenation in presence of Adams catalyst resulted in reduction of the nitro group and simultaneous lactamization yielding the diquinolone (IV) with infra-red absorption at 6·02 μ



III



IV

[1] R. Robinson and H. J. Teuber, *Chem. & Ind.* 783 (1954).
[2] R. H. F. Manske and H. L. Holmes, *The Alkaloids* Vol. II, p. 435. Academic Press (1952).
[3] Reference 17 in B. Witkop and R. K. Hill, *J. Amer. Chem. Soc.* **77**, 6592 (1955); J. E. Saxton, *Quart. Revs.* **10**, 119 (1956).
[4] J. A. Aeschlimann, *J. Chem. Soc.* 2902 (1926).

(amide), and the latter on distillation with zinc dust yielded quinolino(4′:3′-3:4)quinoline, identical with an authentic sample of calycanine.

EXPERIMENTAL

Infra-red spectra were measured as Nujol mulls in a Perkin–Elmer Infracord spectrophotometer by Mr. S. Selvavinayakam.

o-Nitrophenylacetyl isatin. A suspension of sodioisatin[5] (9·5 g) in benzene (60 ml) was treated (stirring) with a solution of *o*-nitrophenylacetyl chloride (from 10 g *o*-nitrophenylacetic acid) in benzene (40 ml). Stirring at 30° was continued for 1 hr and the mixture was then refluxed (stirring) for another hour. The solution was filtered and the residue washed with hot benzene. Evaporation of the combined filtrates yielded the crude *o*-nitrophenylacetyl isatin, used for the next step.

3-o-Nitrophenyl-2-quinolone-4-carboxylic acid. The above crude N-acyl isatin was repeatedly digested with warm 2 N NaOH until no more went into solution and then filtered, cooled, and acidified with HCl. The precipitated acid was filtered and crystallized from methanol (6·9 g), m.p. 322° (decomp) (Found: C, 61·9; H, 3·2. $C_{16}H_{10}O_5N_2$ requires: C, 61·9; H, 3·2%).

The diquinolone IV. The above acid (0·3 g) in alcohol (50 ml) was hydrogenated at 40–50 lbs/in² in presence of Adams catalyst (0·1 g) for 3 hr. The greenish solid was filtered, extracted with hot dimethylformamide and filtered. Dilution of the cooled filtrate with methanol yielded the *diquinolone* (0·2 g) as a yellow crystalline powder, which did not melt at 360°. The yield was considerably lowered if the reduction was carried out in larger batches. The analytical values for this compound agreed for the monohydrate after drying at 100°/2 mm (Found: C, 68·7, 68·7; H, 3·8, 3·9; N, 10·4. $C_{16}H_{10}O_2N_2 \cdot H_2O$ requires: C, 68·6; H, 4·3; N, 10·0%). After prolonged drying at 140° the following values were obtained (Found: C, 70·1; H, 3·7. $C_{16}H_{10}O_2N_2$ requires: C, 73·3; H, 3·8%).

Calycanine. The above diquinolone (0·1 g) was intimately ground with zinc dust (1·5 g) and the mixture covered with a layer of zinc dust (1·5 g). The mixture was heated and the sublimate (7 mg) collected on a cold thumb. The combined sublimate from four batches was crystallized from pyridine–methanol and again sublimed at atmospheric pressure to yield *quinolino*(4′:3′-3:4)*quinoline* (8 mg), m.p. and mixed m.p. with authentic calycanine 310°. Their infra-red spectra were also superposable. (Found: C, 83·0; H, 4·6. Calc. for $C_{16}H_{10}N_2$: C, 83·5; H, 4·3%).

Acknowledgement—We are profoundly grateful to Dr. R. H. Manske for an authentic sample of calycanine, and to Prof. C. L. Stevens (Wayne State University, Detroit) and Mr. S. Selvavinayakam for the analyses. We thank the Government of India and the Council of Scientific and Industrial Research for fellowships (to K. W. G. and S. R.).

[5] G. Heller, *Ber. Dtsch. Chem. Ges.* **40**, 1291 (1907).

Tetrahedron, 1960, Vol. 8, pp. 293 to 295. Pergamon Press Ltd. Printed in Northern Ireland

THE ALKALOIDS OF *ZANTHOXYLUM RHETSA* DC

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(*Received* 11 *August* 1959)

Abstract—The isolation of (±)-evodiamine and the new quaternary alkaloid hydroxyevodiamine from *Zanthoxylum rhetsa* is described.

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Zanthoxylum rhetsa DC syn *Zanthoxylum budrunga* Wall (Rutaceae) has been the subject of several previous chemical investigations. Khastagir[1] reported the isolation from the bark of this tree, of two alkaloids, budrungaine and budrunginine. Gupta and Seshadri[2] isolated from the heartwood suberosin and skimmianine. From the bark, however, they could isolate only lupeol and no alkaloids.

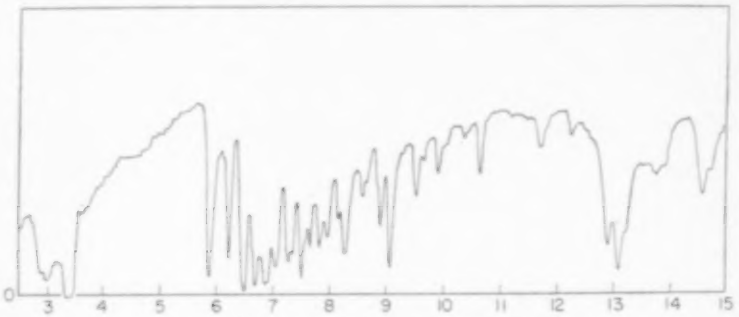
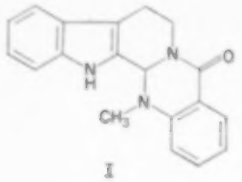


FIG. 1. Dehydroevodiamine chloride (Niyol mull).

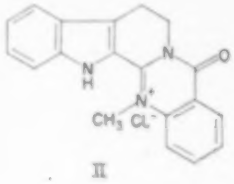
In an investigation of the bark collected from Kerala, the presence of lupeol as reported by Gupta and Seshadri was confirmed. In addition, two nitrogen-containing substances were isolated, one of which was basic and the other neutral. The basic product was isolated from the alcoholic extract of the plant, in the form of its chloride, $C_{19}H_{16}ON_3Cl$, m.p. 256–257°, with infra-red absorption (Fig. 1) at 3·0 μ (>NH), 5·86 μ ($C = \overset{+}{N}<$) and 6·2 μ (benzenoid ring). The chloride on basification with ammonia yielded a base $C_{19}H_{17}O_2N_3$ m.p. 206–207°. On reduction with sodium borohydride the chloride yielded a neutral compound $C_{19}H_{17}ON_3$, m.p. 277–278° with infra-red absorption (Fig. 2) at 3·1 μ (>NH) 6·12 μ (tertiary amide) and 6·20 μ (benzenoid ring). It is interesting to note that the chloride does not have the infra-red band at 6·12 μ; evidently the additional double bond present in the chloride shifts it to longer wavelength so that it merges with the benzenoid absorption at 6·2 μ. The reduction product was found to be identical with (±)evodiamine (I). Further confirmation was obtained by hydrolysis of the reduction product with alcoholic HCl when a compound $C_{19}H_{19}O_2N_3$, m.p. 146–147° yielding a hydrochloride, m.p. 256–257°

[1] H. Khastagir, *Curr. Sci.* **16**, 185 (1947).
[2] V. N. Gupta and T. R. Seshadri, *J. Sci. Industr. Res. India* **16C**, 71, (1957).

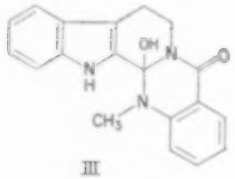
resulted, corresponding to isoevodiamine and its hydrochloride. The chloride should therefore be dehydroevodiamine chloride (II) and the base, hydroxyevodiamine (III). III has not been isolated from any natural source but has been obtained by Asahina



I



II



III

and Ohta[3] by the mild oxidation of evodiamine with potassium permanganate in acetone solution.

(±)-Evodiamine was obtained from the acid-insoluble resin left after the removal of hydroxyevodiamine. Although furanoquinoline,[2] 1 : 2-benzophenanthridine[4] and

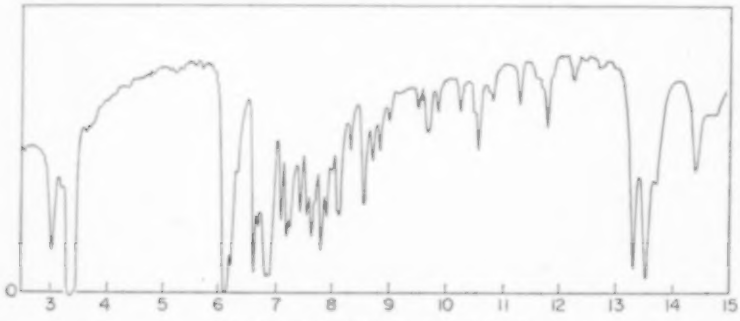


FIG. 2. (±)-Evodiamine (Nujol mull).

protoberberine[5] alkaloids have been isolated from plants belonging to the genus Zanthoxylum, this appears to be the first reported occurrence, in a plant belonging to this genus, of an indoloquinazoline alkaloid, hitherto encountered only in various species of Evodia.

EXPERIMENTAL

Extraction of Zanthoxylum rhetsa. The air-dried powdered bark (13·5 kg) was percolated in cold with light petroleum ether (b.p. 40–60°) for three days and the extract decanted. The process was repeated three times and the combined extract distilled to remove the solvent. The yellow residue was triturated with acetone and the pale yellow solid (400 g) filtered. Several crystallizations of the solid

[3] Y. Asahina and T. Ohta, *J. Pharm. Soc. Japan* No **530**, 293 (1926).
[4] H. R. Arthur, W. H. Hui and Y. L. Ng, *Chem. & Ind.* 1514 (1958).
[5] H. A. D. Jowett and F. L. Pyman, *J. Chem. Soc.* **103**, 291, (1913).

from methanol yielded lupeol, m.p. and mixed m.p. with an authentic sample 211–212°. The acetate obtained by heating the compound with acetic anhydride in pyridine at 100° crystallized from dil ethanol in colourless needles, m.p. 215°, undepressed by mixing with an authentic sample of lupeol acetate.

After extraction with light petroleum ether, the plant material was next extracted in cold alcohol containing 1% acetic acid. The deep yellow alcoholic extract was concentrated to a syrup (water bath) and treated with dil HCl (1 N; 1600 ml). The solution was filtered from the insoluble resin and allowed to remain in a refrigerator for several days when yellow crystals (30 g) deposited. Crystallization from ethanol yielded *dehydroevodiamine chloride* as fine yellow needles, m.p. 255–256° (Ohta[6] reports m.p. 255–256°). (Found: C, 67·6; H, 5·0; N, 12·1. Calc. for $C_{19}H_{16}ON_3Cl$: C, 67·6; H, 4·7; N, 12·4%). The free base was prepared from the chloride by grinding with conc ammonia. The solid obtained was crystallized from ethanol to give fine yellow plates of *hydroxyevodiamine*, m.p. 206–207°. (Found: C, 71·9; H, 5·6; N, 12·7. $C_{19}H_{17}O_2N_3$ requires: C, 71·4; H, 5·3; N, 13·1%).

The insoluble resin left behind after acid extraction was triturated with acetone. The pale yellow amorphous powder (45 g) left behind was crystallized several times from ethyl acetate–methanol yielding (±)-evodiamine as colourless plates m.p. 277–278°; $[\alpha]_D = 0°$ (Asahina and Ohta[7] report m.p. 277–278°). (Found: C, 75·5; H, 5·9. Calc. for $C_{19}H_{17}ON_3$: C, 75·2; H, 5·6%).

Sodium borohydride reduction of dehydroevodiamine chloride. The chloride (0·2 g) dissolved in methanol (30 ml) was treated at room temperature with sodium borohydride (0·2 g) in small lots. The yellow colour of the solution was discharged and a colourless solid separated. After remaining for ½ hr the solid was filtered and washed with methanol. Crystallization from ethyl acetate–methanol yielded (±)-evodiamine (0·1 g) as colourless needles, m.p. and mixed m.p. with the sample of evodiamine obtained from the plant source 277–278°. Their infra-red spectra were also superposable.

Isoevodiamine. (±)-Evodiamine (0·2 g) was heated under reflux with alcoholic HCl (5%; 40 ml) for 3 hr. The solution was concentrated to a small volume and allowed to cool. The colourless crystals that separated were crystallized from ethanol to yield colourless needles of isoevodiamine hydrochloride, m.p. 256–257°. (Asahina and Ohta[7] report m.p. 256–257°.)

The base liberated from the hydrochloride by treatment with ammonia crystallized from dil ethanol in fine needles, m.p. 146–147°. (Asahina and Ohta[7] report m.p. 146–147°). (Found: C, 70·6; H, 6·0. Calc. for $C_{19}H_{19}O_2N_3$: C, 71·0; H, 5·9%).

Acknowledgement—We are grateful to Dr. B. G. L. Swamy, Chief Professor of Botany, Presidency College, Madras, for help in the collection and identification of plant material. We also thank the Government of India for a National Research Fellowship (to K. W. G.) and Mr. S. Selvavinaxakam for microanalyses and infra-red spectra.

[6] T. Ohta, *J. Pharm. Soc. Japan* **65**, No 2A, 15 (1945).
[7] Y. Asahina and T. Ohta, *Ber. Dtsch. Chem. Ges.* **61**, 319 (1928).

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STUDIES ON THE SYNTHESES OF HYDROGENATED QUINOLINES AND ISOQUINOLINES AS ANALGESICS—XVI*

SYNTHESIS OF N-METHYL-8-AZA-DES-N-MORPHINAN (4-METHYL-5:10b-TRIMETHYLENE-1:2:3:4:4a:5:6:10b-OCTAHYDROBENZO [*f*] QUINOLINE)

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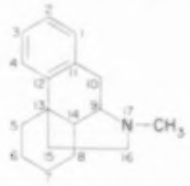
(*Received* 25 *June* 1959)

Abstract—N-Methyl-8-aza-des-N-morphinan (X) was obtained by reducing N-methyl-10-oxo-8-aza-des-N-morphinan (X) prepared by cyclizing 1-methyl-8-hydroxycarbonyl-10-phenyl-decahydro-quinoline (VIII). Recent studies[1] on the synthesis of isomeric morphinans in which the nitrogen in N-methyl-morphinan (A) has migrated to positions other than 17.



A

des – N – Morphinan

OF the nine possible isomers (nitrogen in 5, 6, 7, 8, 9, 10, 14, 15, or 16 position), Sugimoto *et al.* have prepared those with nitrogen in position 6, 7, 9, or 16,[1] and Ochiai *et al.* prepared 15-aza-des-N-morphinan.[2] Pharmacological examination of these compounds was carried out. With the exception of 9-aza-des-N-morphinan, the isomers were all synthesized by formation of the B-ring, by rearrangement-cyclization of benzyloctahydro-isoquinoline or quinoline. It had been shown that the steric configurations of these synthetic compounds is the same as that of morphinan with B/C *cis* and C/D *trans*. Of these five compounds, the one with hydroxyl in 3-position and nitrogen in 9-position was found to have analgesic action equally strong as morphine, and 7-aza-des-N-morphinan was found to have analgesic activity, though weak, but 6, 15, and 16-aza-des-N-morphinans were entirely devoid of any physiological activity.

In the present work, attempted synthesis of N-methyl-8-aza-des-N-morphinan (X), was carried out by the route indicated in Chart 1. Boekelheide,[3] Backmann,[4] and

* Part XV. N. Sugimoto, *Chem. Pharm. Bull.* **6**, 429 (1958).

[1] N. Sugimoto and H. Kugita, *Pharm. Bull. Japan* **3**, 11 (1955); N. Sugimoto and S. Ohshiro, *Ibid.* **4**, 353, 357 (1956); N. Sugimoto, S. Ohshiro, H. Kugita, and S. Saito, *Ibid.* **5**, 62 (1957); N. Sugimoto and H. Kugita, *Ibid.* **5**, 67 (1957); N. Sugimoto and S. Ohshiro, *Ibid.* **5**, 316 (1957); N. Sugimoto and H. Kugita, *Ibid.* **5**, 378 (1957); N. Sugimoto and H. Kugita, *Ibid.* **6**, 429 (1958).

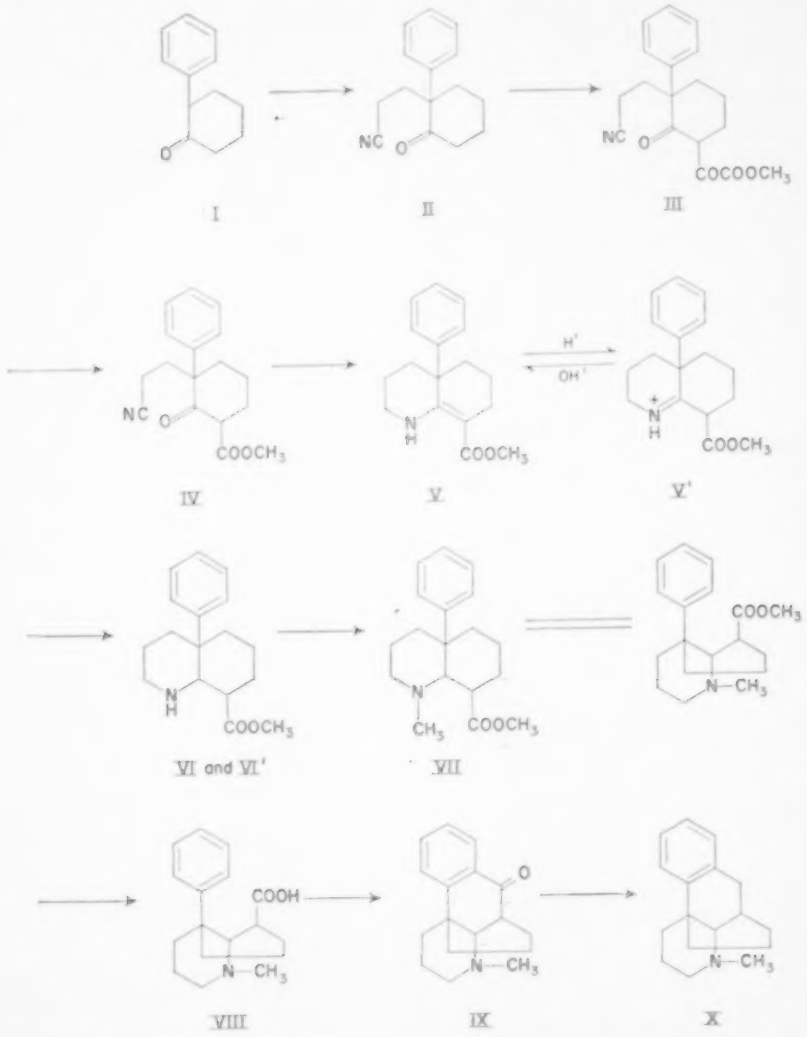
[2] E. Ochiai and K. Harasawa, *Pharm. Bull. Japan* **3**, 369 (1955).

[3] V. Boekelheide, *J. Amer. Chem. Soc.* **69**, 790 (1947).

[4] V. B. Backmann, *J. Amer. Chem. Soc.* **72**, 3388 (1950).

Sugimoto[5] had obtained 2-(β-cyanoethyl)-2-phenyl-cyclohexanone (II) by cyanoethylation of 2-phenylcyclohexanone (I). Condensation of II with methyl oxalate[6] yielded (III), which on pyrolysis gave the ketoester (IV), showing characteristic absorptions for a nitrile and β-keto-ester at 2252, 1755, 1720, 1660, and 1625 cm^{-1} (Fig. 1). Catalytic reduction of IV with Raney nickel gave the ester (V).

The structure of the ester (V) was confirmed chemically as well as by analysis and infra-red absorption spectrum.[7] In the infra-red spectrum (Fig. 2) of V, the absorption for C≡N had disappeared and instead showed absorption for —NH at 3250 cm^{-1} and for an α,β-unsaturated ester at 1650 and 1600 cm^{-1}. The infra-red spectrum of



[5] N. Sugimoto, H. Kungita and T. Fujita, *J. Pharm. Soc. Japan* **75**, 177 (1955).
[6] W. B. Backmann and L. B. Wick, *J. Amer. Chem. Soc.* **72**, 1995 (1950).
[7] K. Ohsugi, *J. Pharm. Soc. Japan* **79**, 1313 (1958).

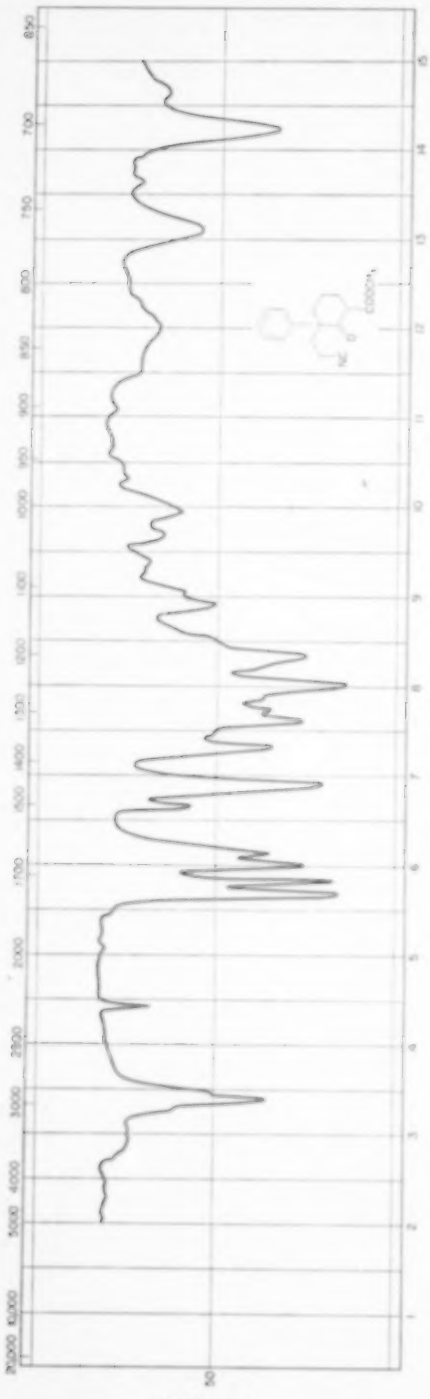


FIG. 1.

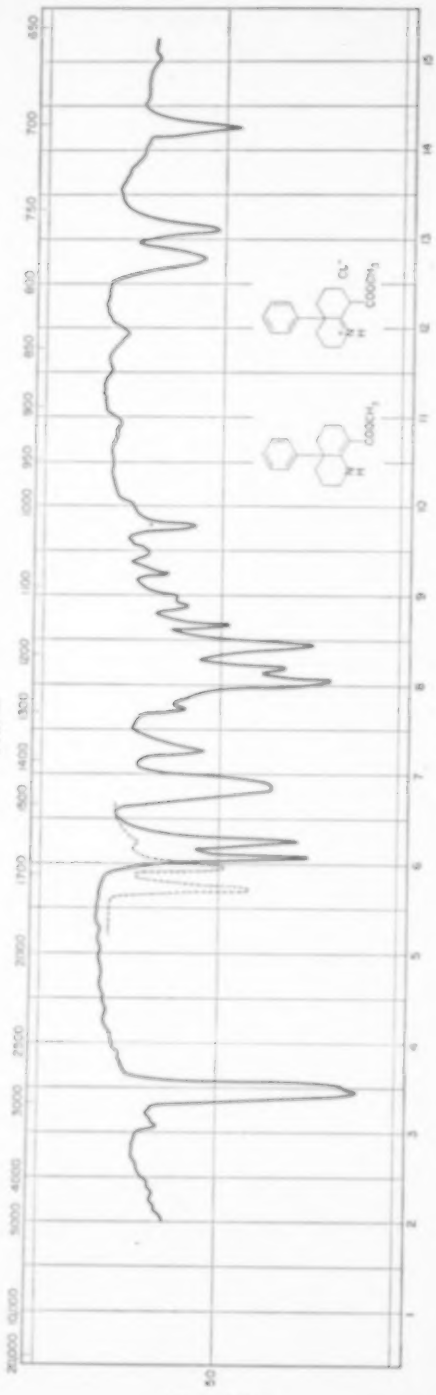


FIG. 2.

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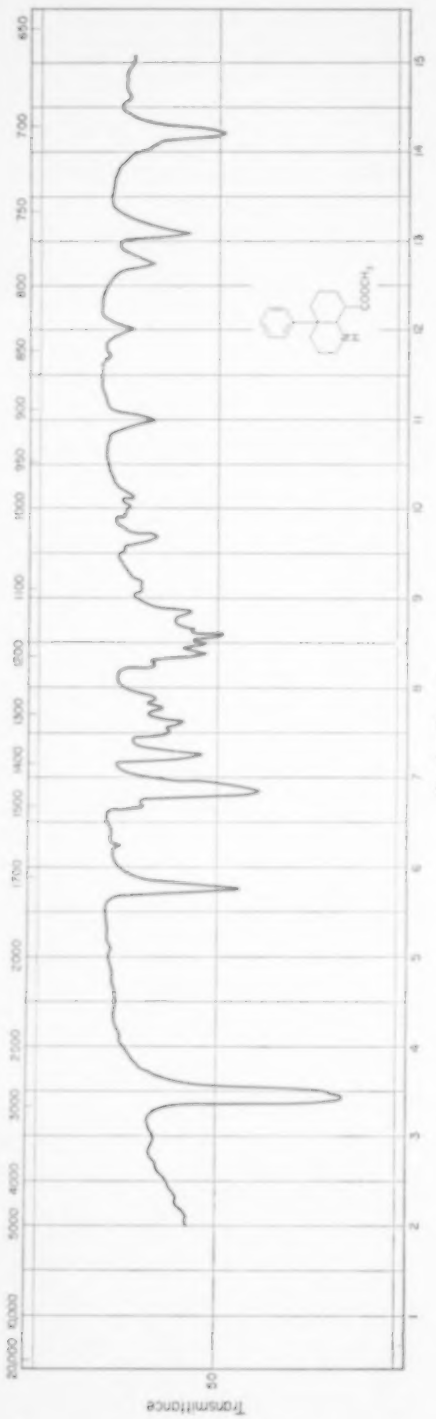

FIG. 3.

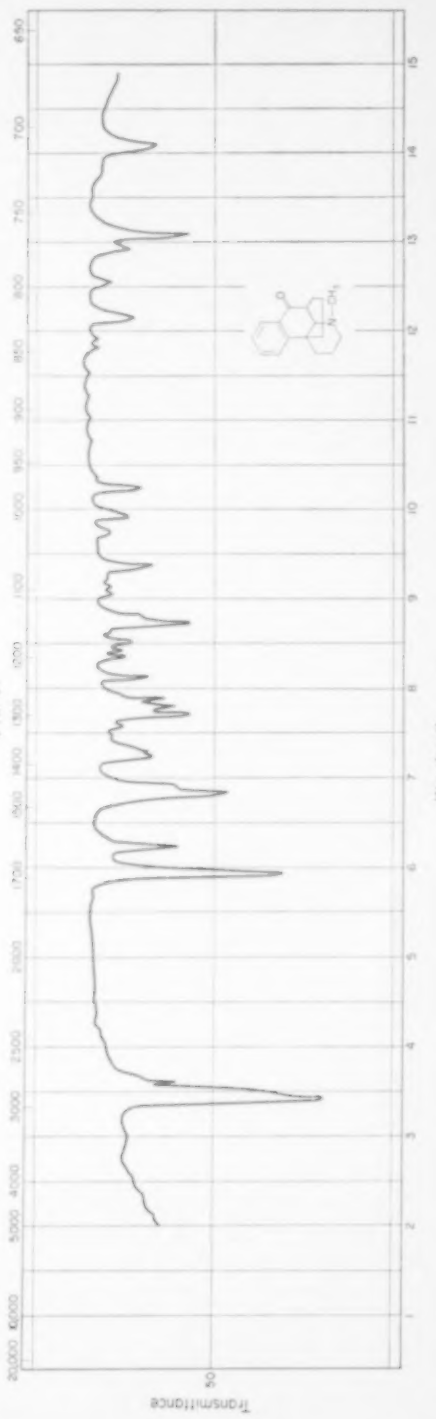

FIG. 4.

its hydrochloride (Fig. 2) exhibits absorption for non-conjugated ester at 1745 cm^{-1} and ketimine —C=$\overset{+}{\underset{H}{N}}$— at 1685 cm^{-1}. Ferric chloride gives no reaction with V but on heating V with dilute hydrochloric acid demethoxycarbonylation takes place with evolution of carbon dioxide.

Hydrogenation of V in neutral medium, over platinum oxide, failed to effect reduction, but in acid medium, catalytic reduction of V was effected quite easily at ordinary temperature and pressure, and 1 mole of hydrogen was absorbed smoothly

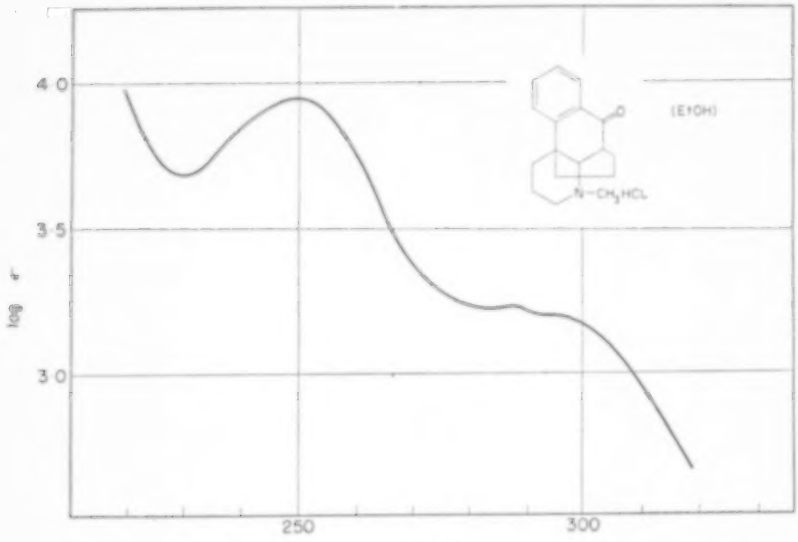

FIG. 5.

to form (VI). The infra-red spectrum of VI no longer exhibited absorption of an α,β-unsaturated ester but absorption of a non-conjugated ester was observed at 1740 cm^{-1} (Fig. 3). A crystalline hydrochloride (VI–HCl) is readily formed together with a small amount of non-crystalline hydrochloride (VI′–HCl). Methylation of VI–HCl by the conventional method yielded the N-methyl compound VII. Attempted cyclization of VII with polyphosphoric acid failed with recovery of the starting compound and VII also resisted saponification with ethanolic potassium hydroxide. Saponification was finally effected by heating with concentrated hydrochloric acid for 20 hours. The hydrochloride of (VIII) obtained was heated with polyphosphoric acid 10 hours and the cyclized product (IX) obtained. Its infra-red spectrum no longer showed characteristics of the ester but exhibited the absorption of an aromatic ketone at 1690 cm^{-1} (Fig. 4).[8] The UV spectrum of IX showed absorption maxima at 250 mμ (log ε 3·945) and at 287 mμ (log ε 3·228).[8] These facts indicated that IX is N-methyl-10-oxo-8-aza-des-N-morphinan (Fig. 5).

The Huang-Minlon reduction of the hydrazone of IX resulted in the formation of N-methyl-8-aza-des-N-morphinan (X) whose infra-red spectrum no longer showed

[8] C. D. Gutsche, *J. Amer. Chem. Soc.* **73**, 786 (1951).

absorption for an aromatic ketone (Fig. 6). Analysis also proved the formation N-methyl-8-aza-des-N-morphinan.

Structure and steric configuration of X will be described in detail in the following report.

EXPERIMENTAL

2-(β-Cyanoethyl)-2-phenyl-6-methoxycarbonyl-cyclohexanone (IV). Methanol free sodium methylate prepared from sodium (2·3 g) and methanol, was suspended in benzene (60 cc) and to this solution methyl oxalate (11·8 g) was added. Phenyl-cyclohexanone-nitrile (II, 11·3 g) in benzene (70 cc) was added dropwise to the above homogeneous mixture. The mixture was kept below 5° during the addition, which required about 2 hr. The mixture was allowed to stand overnight at room temp, and then decomposed with ice-water. The aqueous layer was separated, acidified to congo red with hydrochloric acid and extracted with ether. After removal of the solvent, a red brown oil remained which was heated with finely powdered glass in an oil-bath at 160–170° under nitrogen. Evolution of carbon monoxide was complete after 10 min, and heating continued for further 15 min.

After cooling, the reaction mixture was extracted with benzene, washed with water and dried. After evaporation of the solvent, the residue was distilled giving the keto ester (IV, 8·2 g, 58%) as a pale yellow viscous oil, b.p. 195–198°/0·9 mm.

Ethanol solution of IV gave an orange yellow colour for enol test with $FeCl_3$.

8-Methoxycarbonyl-10-phenyl-1,2,3,4,5,6,7,10-octahydroquinoline (V). A mixture of keto ester (IV, 3·0 g), Raney-Ni (5·0 g), liq. ammonia (2 g) and ethanol (200 ml) sealed in a stainless steel bomb was hydrogenated in 76 atm at 150°. Absorption of hydrogen was completed after 6 hr and after cooling, the filtrate was evaporated under diminished pressure and the residue recrystallized from methanol. Methl octahydroquinoline-carboxylate (V, 1·8 g 66·2%) was obtained as colorless plates, m.p. 106–107·5.

The ethanol solution of V gave negative enol test with $FeCl_3$.

(Found: C, 75·24; H, 7·8; N, 5·16. $C_{17}H_{21}NO$ requires: C, 75·6; H, 7·8; N, 5·1%).

8-Methoxycarbonyl-10-phenyl-decahydroquinoline (VI). A solution of V (10 g) dissolved in ethanol (200 ml) and 26% ethanolic hydrogen chloride (17 ml) was hydrogenated at atmospheric pressure using PtO_2 (0·2 g). After 10 min, one equivalent (930 ml) of hydrogen was absorbed and further absorption was not observed. The filtrate from catalyst was evaporated under reduced pressure, and the residue was recystallized from methanol–ether to give 9·1 g of VI–HCl as colorless needles m.p. 243° (dec).

(Found: C, 65·91; H, 7·75; N, 4·52. $C_{17}H_{24}NO_2Cl$ requires; C, 65·8; H, 7·8; N, 5·1%).

Evaporation of the mother liquor left a non-crystalline hydrochloride (0·9 g) identification as isomer of VI–HCl will be reported in the following paper.

Free base VI was obtained by neutralization of its hydrochloride with aqueous potassium carbonate and recrystallized from methanol to give colorless columns m.p. 73–75°.

(Found: C, 74·69; H, 8·48; N, 5·12. $C_{17}H_{23}NO_2$ requires: C, 74·6; H, 8·6; N, 5·6%).

1-Methyl-8-methoxycarbonyl-10-phenyl-decahydroquinoline (VII). VI was methylated by the usual technique. The decahydro compound VI–HCl (0·5 g) was heated with 80 % formic acid (15 ml), 35% formaline solution (4·0 g) and sodium formate (0·68 g) at 95° for 10 hr. The mixture was evaporated to dryness under diminished pressure, and the residue was made alkaline with aqueous ammonia. The separated solid was filtered, washed with water and dried. Recrystallization of the residue from methanol gave colorless plates, m.p. 106–108°.

(Found: C, 75·22; H, 8·77; N, 4·87. $C_{18}H_{25}NO_2$ requires: C, 75·25; H, 8·7; N, 4·87%).

Hydrochloride; colorless plates (from methanol–ether), m.p. 242 (dec).

(Found: C, 66·75; H, 8·04; N, 4·33. $C_{18}H_{26}NO_2Cl$ requires: C, 66·5; H, 8·0; N, 4·5%).

N-Methyl-10-ox-8-aza-des-N-morphinan (IX). VII 5·2 g) was heated to boiling with HCl (50 ml) for 8 hr. Then, after addition of HCl (50 ml), heating was continued for 8 hr. The mixture was evaporated to dryness under reduced pressure, and the residue basified with 10 % aqueous sodium hydroxide and extracted with ether from which a small amount of starting material was recovered. The aqueous layer was again acidified with conc HCl, and evaporated to dryness.

Polyphospholic acid prepared from P_2O_5 (36 g) and 85 % H_3PO_4 (36 ml) was added to the above

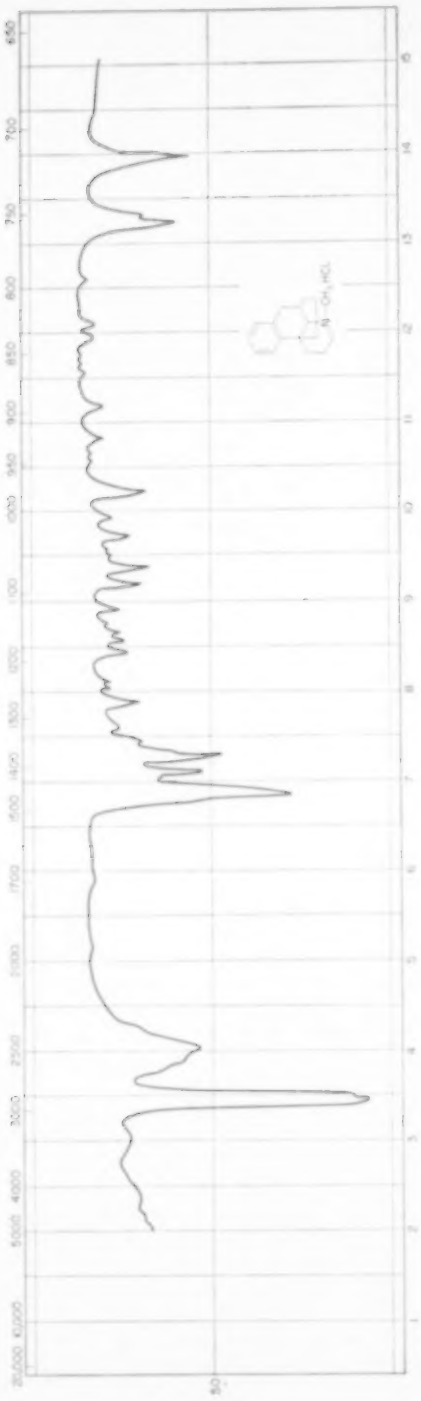

FIG. 6.

crude VIII–HCl, and the mixture was heated (oil bath) at 130–140° for 10 hr. The reaction mixture was poured on crushed ice, and basified with 30% aqueous potassium hydroxide below 10°. The alkaline mixture was extracted with ether, washed with water, and dried. After evaporation of the solvent, the residue was purified by distillation giving IX (2·9 g, 62·5%) of colorless viscous oil b.p: 170–175°/0·1 mm. The distillate solidified on treatment with methanol and recrystallization from this solvent gave colorless plates, m.p. 96–98°.

(Found: C, 79·96; H, 8·29; N, 5·49. $C_{17}H_{21}NO$ requires: C, 79·9; H, 8·2; N, 5·9%).

Hydrochloride: colorless plates (from methanol–ether), m.p. 159° (dec).

(Found: C, 65·91; H, 7·75; N, 4·52. $C_{17}H_{22}NOCl{\cdot}H_2O$ requires: C, 66·35; H, 7·85 N, 4·3%).

IX was heated with 85% hydrazine hydrate in boiling ethanol for 3 hr, to give the *hydrazone* which formed colorless plates, from aqueous ethanol, m.p. 154–156°.

(Found: C, 75·79; H, 8·61; N, 15·6. $C_{17}H_{23}N_3$ requires: C, 75·9; H, 8·25; N, 15·4%).

N-*Methyl*-8-*aza*-*des*-N-*morphinan* (X). When IX (0·5 g), and 85% hydrazine hydrate (0·3 ml) were heated (steam bath) for a few minutes, the colorless hydrazone separated. After heating for 1 hr, finely powdered potassium hydroxide (0·5 g) and propylenglycol (5 ml) were added and heating continued at 170–180° (bath temp) for 10 hr.

The mixture was cooled, diluted with water and extracted with ether, the extracts were evaporated and the residue distilled to give 0·2 g of X as a colorless viscous oil which b.p. 155–165° (bath temp)/0·1 mm.

Hydrochloride: colorless needles (from methanol–ether), m.p. 274–276° (dec)

(Found: C, 73·51; H, 8·6; N, 5·05. $C_{17}H_{24}NCl$ requires: C, 73·55; H, 8·55; N, 5·05%).

The *methiodide* was prepared from X and excess methyl iodide in methanol and it formed colorless columns from methanol, m.p. 267° (dec).

(Found: C, 56·2; H, 6·8; N, 3·65 $C_{18}H_{27}NI$ requires: C, 56·05; H, 6·55; N, 3·7%).

Acknowledgements—The authors are indebted to Mr. K. Kodera of this Laboratory for infra-red spectral measurement and to Mrs. F. Hisamichi and Messrs. T. Yoda and T. Kawano for elemental analyses.

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STUDIES ON THE SYNTHESES OF HYDROGENATED QUINOLINES AND ISOQUINOLINES AS ANALGESICS—XVII[1]

THE STERIC STRUCTURE OF N-METHYL-8-AZA-DES-N-MORPHINAN

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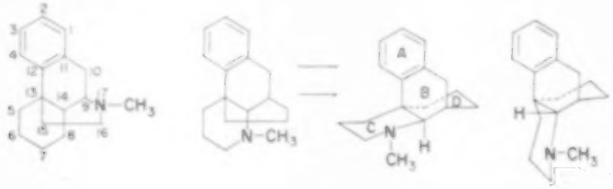
(*Received* 25 *June* 1959)

Abstract—The configuration of positions 13 and 14 in N-methyl-8-aza-des-N-morphinan[1] has been investigated. Potassium t-but-oxide in t-butanol converts N-acetyl-10-oxo-8-aza-des-N-morphinan (XVI) into 10-hydroxy-8,10-(α-oxo-ethano)-8-aza-des-N-morphinan (XVII). Formation of these new lactams is possible only when rings B and C are *cis*. It follows, therefore, that 8-aza-des-N-morphinan synthesized in this investigation has B/C in *cis* and C/D in *trans* positions the same as the steric structure of morphinan (M).



M XIII a XIII b

THE series of des-N-morphinan compounds with nitrogen shifted to position 6, 7, 9, 15, or 16 reported since 1955 are all compounds of morphinan type.

Condensation of 2-(β-cyanoethyl)-2-phenylcyclohexanone (I) with methyl oxalate, in the presence of sodium methoxide, and subsequent decarbonylation yielded the keto ester (III) which on reduction give methyl octahydroquinol-inecarboxylate (IV). In this case, only one ester was obtained and no isomers were detected. Heating of IV with dilute hydrochloric acid effects demethoxy-carbonylation to form octahydroquinoline (V) whose infra-red spectral analysis indicates absorptions for —NH— at 3250 cm^{-1} and for —C=CH— at 1660 cm^{-1} in neutral medium, and an absorption for $-C=\overset{+}{N}H-$ of ketimine at 1692 cm^{-1} in acid medium (V′), showing V to be an α,β-unsaturated amine.[2] Catalytic reduction of V′ at ordinary pressure, using platinum oxide, results in rapid absorption of one mole of hydrogen to form decahydroquinoline (VI). The infra-red spectrum of VI failed to show the absorption of an α,β-unsaturated amine and that this compound is represented by the structure VI was proved by mixed m.p. of its picrate with that of 10-phenyldecahydroquinoline previously synthesized by Sugimoto *et al.*[3]

[1] Part XVI: N. Sugimoto and S. Ohshiro, *Tetrahedron* **8**, 296 (1960).
[2] N. J. Leonard, *J. Amer. Chem. Soc.* **78**, 3463 (1956).
[3] N. Sugimoto, H. Kugita and T. Fujita, *J. Pharm. Soc. Japan* **75**, 177 (1955); N. Sugimoto and H. Kungita, *Pharm. Bull. Tokyo* **5**, 378 (1957).

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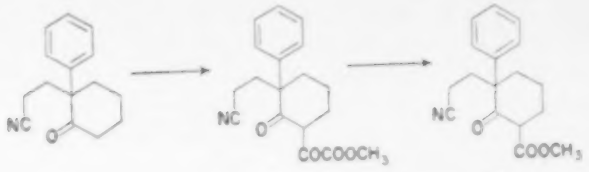
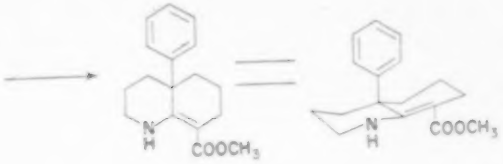
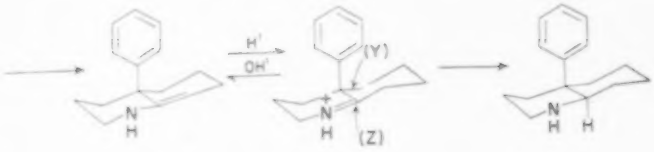


I II III



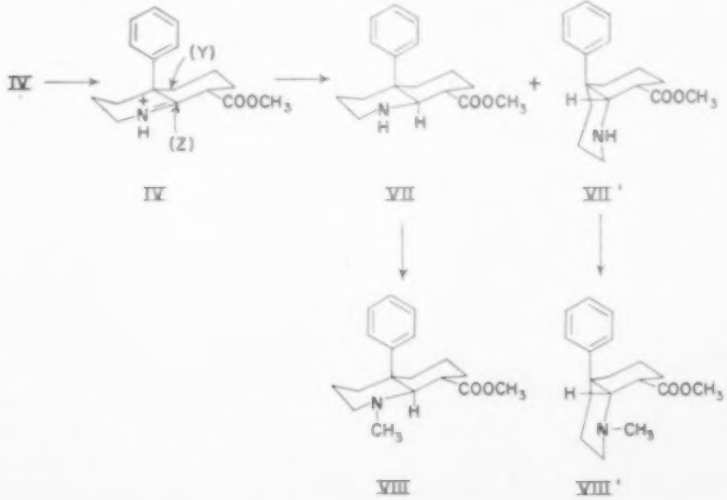
IV



V V' VI

In the catalytic reduction of octahydroquinoline (V'), addition of hydrogen could take place from the direction of either Y or Z but the addition of hydrogen from direction Z with less steric hindrance seems theoretically more probable. The fact that only one product has been obtained makes it certain that VI is a *trans* compound.

Examination of molecular a model has shown that the conformation of compound IV has the 10-phenyl group axial to octahydroquinoline and the methoxycarbonyl

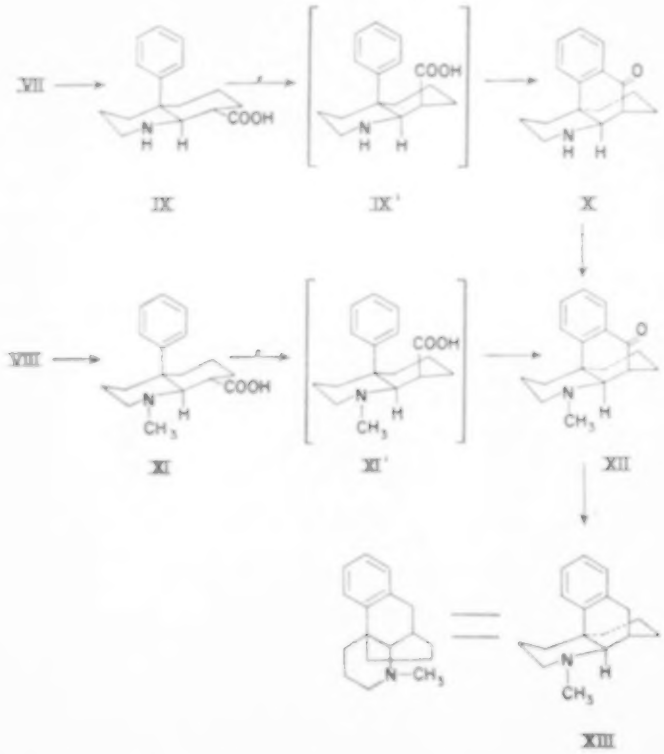


IV VII VII' VIII VIII'

group on the same plane as the octahydroquinoline. In acid medium, the double bond in conjugation with methoxycarbonyl would form ketimine (IV) by prototropy with the imino group and excluded from conjugation with the methoxycarbonyl group,[1] and the configuration of the latter on the same plane as octahydroquinoline, would be shifted to *trans* (equatorial) position with regard to the axial phenyl group because it is assumed that the methoxycarbonyl group cannot take a *meta*-diaxial conformation in relation to the large molecule of phenyl in the axial position.

Hydrogenation of the ketimine (IV′) yielded two isomers VII and VII′ indicated by analyses and infra-red spectral analyses. It is clear that in this case, hydrogenation is more likely to be made on the Z side of the equatorial methoxycarbonyl group and not on the Y side of the axial phenyl group. It is assumed that crystalline VII obtained in a larger quantity is the 9,10-*trans* compound and liquid VII′ obtained in a smaller amount is the 9,10-*cis* compound.

Methylation of VII and VII′ gave the methylated compound VIII, m.p. 106–108°, and VIII′ of m.p. 95–96° respectively. A mixture of the two showed a m.p. depression.



Cyclization of ester (VIII) with polyphosphoric acid and saponification by heating with ethanolic or aqueous sodium hydroxide failed,[1] indicating that VIII is a stable compound which does not undergo steric rearrangement.

Saponification of VIII was finally effected with hydrochloric acid and heating of N-methyl-decahydroquinolinecarboxylic acid (XI) so formed with polyphosphoric acid

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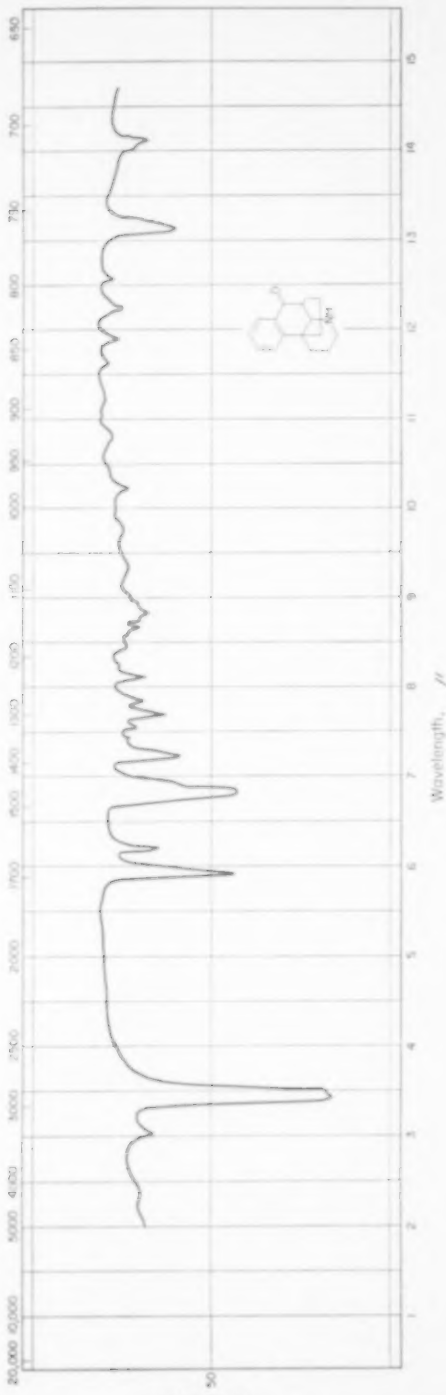


Fig. 1.

gave N-methyl-10-oxo-des-N-morphinan (XII).[1] It is assumed that, in this case, the carboxyl group of XI undergoes epimerisation by heating, and assumes *meta*-diaxial conformation with the phenyl group, forming XI′ with subsequent cyclization-condensation with the phenyl group to form XII. As stated above, this reaction does not involve rearrangement of the configuration in the decahydroquinoline ring, its *trans* nature being maintained throughout these reactions.

On the other hand, the compound IX was prepared from VII by the same reaction route, and 10-oxo-des-N-morphinan (X) was prepared via the epimer IX′ of IX.

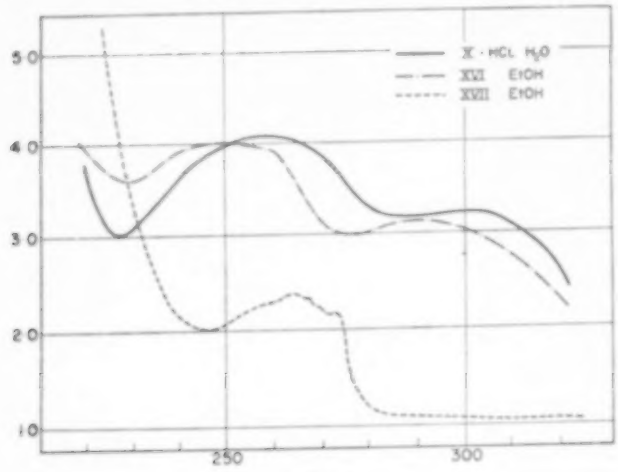
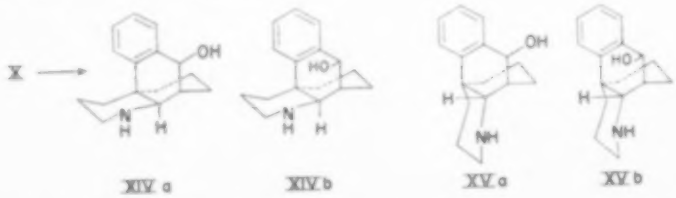


FIG. 2.

Infra-red spectrum of this compound (X) indicated absorptions of =NH at 3300 cm^{-1}, of an aromatic ketone at 1690 cm^{-1}, and an out-of-plane vibration of *ortho*-substituted benzene at 760 cm^{-1} (Fig. 1). The U.V. spectral curve of X exhibits characteristic absorptions of an aromatic ketone (Fig. 2).[4] Methylation of X gives a compound identical with N-methyl-10-oxo-8-aza-des-N-morphinan (XII) previously synthesized.

The preparation of N-methyl-8-aza-des-N-morphinan (XIII) by the Huang-Minlon reduction of XII has been described.[1]



XIV a XIV b XV a XV b

Catalytic reduction of the hydrochloride of X gave 10-hydroxy-8-aza-des-N-morphinan (XIVa m.p. 137–139°), and no isomer was detected. There is a possibility of two isomers, by reduction of the ketone group in quasi-equatorial form (XIVa) and in quasi-axial form (XIVb).

[4] C. D. Gutsche, *J. Amer. Chem. Soc.* **73**, 786 (1951).

In the morphinan-type (XIVa), C^{14}—C^{8} lies axial to the B-ring with hydroxyl in quasi-equatorial conformation, while in XIVb C^{14}—C^{8} lies axial to the B-ring with hydroxyl in quasi-axial conformation. In the isomorphinan-type (XVa), this C^{14}—C^{8} bond lies equatorial to the B-ring, with hydroxyl in quasi-equatorial conformation, and in XVb, the C^{14}—C^{8} is equatorial to the B-ring with hydroxyl in quasi-axial conformation. That XIVb should be the most unstable of all the four possible isomers, is self-explanatory from the fact that it assumes *meta*-diaxial conformation. If XIV is a morphinan type, there is a possibility of the formation of XIVa alone, while if it is an isomorphinan type, it would be possible to expect formation of a mixture of XVa and XVb. Since only one kind of hydroxy compound had been obtained, it is likely that this compound (XIV) is in morphinan-type configuration.

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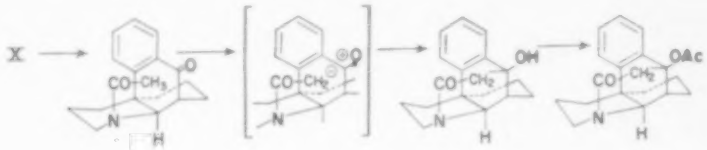
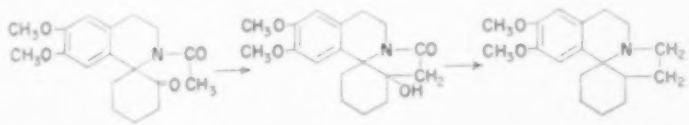


XVI XVII XVIII

Acetylation of X gave XVI whose infra-red and ultra-violet spectral curves are shown in Figs. 3 and 2. Heating of XVI with potassium t-butoxide results in intramolecular proton migration, a piperidone ring being formed. This fact is proved by its infra-red spectrum (Fig. 3) showing absorptions for hydroxyl at 3240 cm^{-1} and a six-membered ring acid amide —NH—CO— at 1620 cm^{-1}, and disappearance of a carbonyl absorption. The ultra-violet spectral curve of XVII (Fig. 2) indicates the disappearance of the characteristic absorption of an aromatic ketone, leaving the absorption of a benzene ring.

Acetylation of XVII afforded the acetoxy compound (XVIII), whose infra-red spectrum (Fig. 4) indicates absorption for ester at 1725 cm^{-1}, and no hydroxy absorption. Such transfer of a proton from acetamide to a ketone with formation of a new ring-lactam is similar to the following reaction which was utilized by Sugasawa and Yoshikawa[5] for the synthesis of erythrinane.



Possibility of condensed-ring formation between the ketone at 10 and acetyl group at 8-position was examined with a model. The results clearly indicate that this reaction is possible only in the morphinan type XIIIa since the distance between the methyl in acetyl and the carbonyl is too great in the isomorphinan type XIIIb.

8-Aza-des-N-morphinan prepared by Sugimoto and Ohshiro[1] is, therefore, a morphinan type XIIIa with B/C in *cis* and C/D in *trans*. At the same time, the steric configurations assumed above for the intermediates formed during the course of these reactions are correct.

[5] S. Sugasawa and H. Yoshikawa, In press.

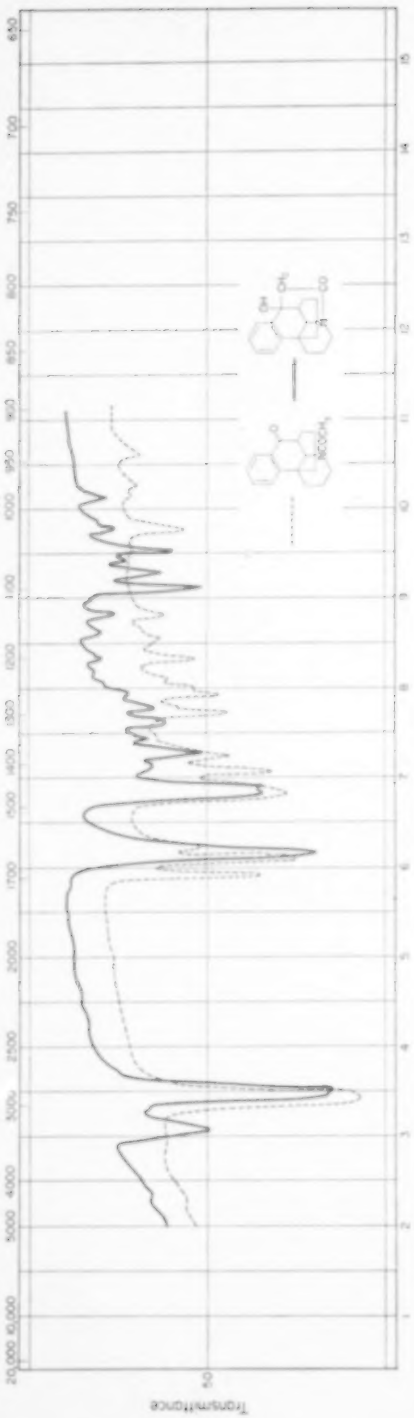


FIG. 3.

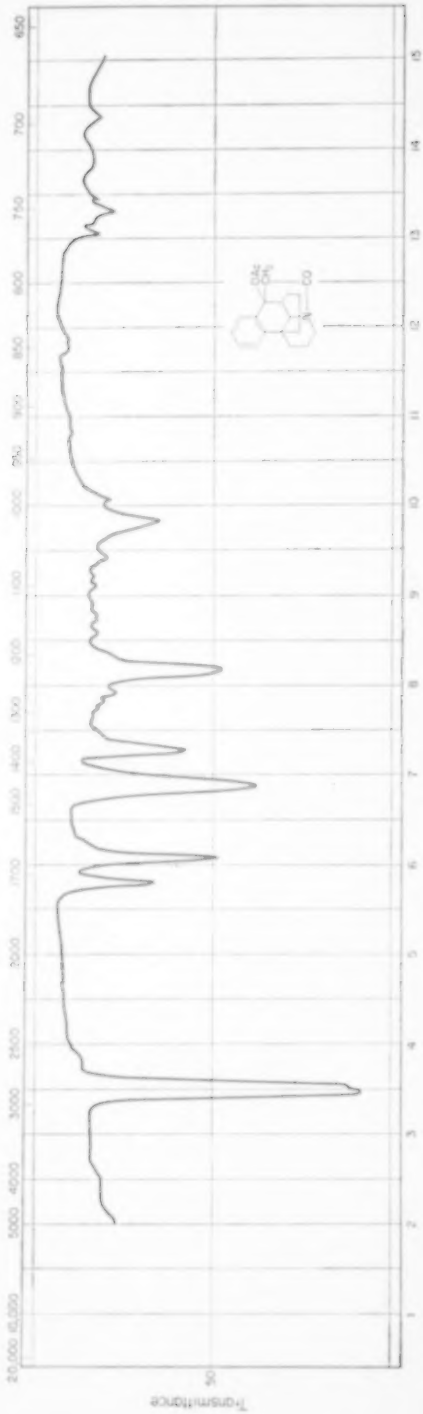


FIG. 4.

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EXPERIMENTAL

10-*Phenyl*-1,2,3,4,5,6,7,10-*octahydroquinoline* (V). Methyl 10-phenyl-octahydroquinoline carbonate (IV, 1·0 g) was dissolved in 20% HCl (7 ml), and heated (steam bath) for 5 hr. The mixture was evaporated to dryness under reduced pressure, and the residue basified with aqueous potassium carbonate. The base (r) was extracted with ether, dried and evaporated and (0·8 g) was obtained as a colorless oil b.p. 115–118°/0·5 mm.

Perchlorate: Recrystallization from aqueous methanol gave colorless plates, m.p. 174–176°.

(Found: C, 57·41; H, 6·38; N, 4·46. $C_{15}H_{20}NO_4Cl$ requires: C, 57·55; H, 6·5; N, 4·4%).

Picrate: yellow needles (from acetone), m.p. 152–153°.

10-*Phenyl-decahydroquinoline* (VI). The V-$HClO_4$ (0·7 g) in ethanol (25 ml) was hydrogenated at atm press with PtO_2 (0·2 g). One equivalent hydrogen (95 ml) was absorbed in 5 min, with no further absorption. The catalyst was filtered and the filtrate concentrated under reduced pressure. Recrystallization of the residue from aqueous methanol gave decahydroquinoline (VI)-$HClO_4$ as colorless columns, m.p. 215–217: a mixed m.p. with an authentic sample[5] showed no depression.

Picrate: yellow needles (from acetone), m.p. 157–158°.

These results indicate that the product VI is identical with the product prepared by Sugimoto.[5]

Isomeric N-*methyl*-8-*methoxycarbonyl*-10-*phenyl-decahydroquinoline* (VIII′). Isomeric decahydroquinoline (VII′, 0·6 g), obtained by hydrogenation of octahydroquinoline (IV) as described in the previous paper, was methylated with formic acid (5 ml) and formalin solution (1 ml). The crude decahydroquinoline (VIII′) was recrystallized from methanol to give colorless plates, m.p. 95–96°. Mixed m.p. with VIII m.p. 106–108° was depressed to 75–80°.

(Found: C, 75·25; H, 8·77; N, 4·87. $C_{18}H_{25}NO_2$ requires: C, 75·2; H, 8·7; N, 5·15%).

10-*Oxo*-8-*aza-des*-N-*morphina* (X). 8-Methoxycarbonyl-10-phenyl-decahydroquinoline hydrochloride (VII)-HCl (0·5 g) was heated to boiling with conc HCl (20 ml) for 10 hr, and the mixture was evaporated under reduced pressure.

The residue, amino acid–HCl (IX) was, without purification, heated (oil bath) at 130–140° for 8 hr, with polyphosphoric acid prepared from 85% H_3PO_4 (6 ml) and P_2O_5 (6 g). The mixture was cooled and diluted with ice-water, and basified with aqueous 30% KOH and chilled below 10°.

The oil was extracted with ether, the combined extracts washed with water, dried, and evaporated. The residue solidified on treatment with ether and recrystallization from this solvent yielded 10-*oxo*-8-*aza-des*-N-*morphinan* (X, 0·15 g) as colorless columns, m.p. 90–92°.

(Found: C, 79·63; H, 7·94; N, 5·80. $C_{16}H_{19}NO$ requires: C, 79·5; H, 7·9; N, 5·75%).

X (120 mg) was methylated with methyl sulfate (60 mg) and powdered potassium carbonate (110 mg) in acetone. Methylated product (from methanol, m.p. 95–97°) was identified by a mixed m.p. with an authentic sample prepared in the previous paper.

N-*Acetyl*-10-*oxo*-8-*aza-des*-N-*morphinan* (XVI). 10-Oxo-8-aza-des-N-morphinan (X, 0·3 g) was acetylated with acetic anhydride (2 ml) and pyridine (1 ml) by heating (steam bath) for 6 hr. The mixture was decomposed with ice-water, and the product recrystallized from ethanol yielding the N-*acetyl derivative* (XVI, 0·3 g) as colorless plates, m.p. 195–197°.

(Found: C, 76·29; H, 7·47; N, 4·94. $C_{18}H_{21}NO_2$ requires: C, 76·4; H, 7·3; N, 5·25%).

10-*Hydroxy*-8,10-(α-*oxo-ethano*)-8-*aza-des*-N-*morphinan* (XVII). XVI (170 mg) in t-buthanol (3 ml) was added to the solution of potassium (50 mg) in t-buthanol (3 ml), and the mixture gently refluxed (water bath) for 5 hr. The solvent was removed and the residue diluted with water repeatedly extracted with ethylacetate. The combined extracts were washed, dried and evaporated.

The residue was purified by repeated recrystallization to give 10-hydroxy-8,10-(α-oxo-ethano)-8-aza-des-N-morphinan (XVII, 130 mg) as colorless columns, m.p. 238–240°.

(Found: C, 76·29; H, 7·47; N, 4·94. $C_{18}H_{21}NO_2$ requires: C, 75·93; H, 7·47; N, 4·97%).

10-*Acetoxy*-8,10-(α-*oxo-dethano*):8-*aza-des*-N-*morphinan* (XVIII). XVII (350 mg) was heated with acetic anhydride (5 ml) and conc H_2SO_4 (0·1 ml) (steam bath) for 10 hr. The mixture was decomposed with ice-water, and the product recrystallized from ether yielding the *acetoxy derivative* (XVIII) as colorless columns, m.p. 188–190°.

(Found: C, 73·83; H, 7·12. $C_{20}H_{23}NO_3$ requires: C, 73·5; H, 7·24%).

10-*Hydroxy*-8-*aza-des*-N-*morphinan* (XIVa). X (0·3 g) was dissolved in ethanol (20 ml) and 17% ethanolic hydrogen chloride (3 ml). This solution was hydrogenated at atm press using PtO_2 (0·1 g) as catalyst. One equivalent (32 ml) of hydrogen was absorbed in 25 min, after which hydrogenation

became slow. The filtrate from the catalyst was distilled and the residue recrystallized from ethanol–ether, giving XIVa-HCl (0·3 g) as colorless needles, m.p. 264° (decom).

(Found: N, 5·01. $C_{16}H_{22}NOCl$ requires: N, 5·35%).

Neutralization of the hydrochloride with aqueous potassium carbonate gave the free base (XIV) which was recrystallized from petroleum ether to give colorless needles, m.p. 137–139°.

(Found: C, 78·96; H, 8·70; N, 5·76. $C_{16}H_{21}NO$ requires: C, 79·2; H, 8·5; H, 5·8%).

Acknowledgements—The authors are indebted to Messrs. K. Kodera and T. Takahashi for infra-red and ultra-violet spectral measurements, and to Mrs. F. Hisamichi and Messrs. T. Yoda and T. Kawano for elemental analyses reported herein.

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THE KINETICS OF THE CHROMIC ACID OXIDATION OF DIPHENYLMETHANE*

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(*Received* 2 *September* 1959)

VOL. 8 1960

Abstract—The kinetics of the chromic acid oxidation of diphenylmethane in aqueous acetic acid solution has been studied. The rate law is

$$v = k[\phi CH_2\phi][CrO_3]h_0$$

a kinetic isotope effect, $k_H/k_D = 6{\cdot}4$ at 30°, was noted, and electron releasing groups were found to moderately facilitate the reaction ($\rho^+ = -1{\cdot}17$). These, and related data, suggest that the initial reaction is the abstraction of a hydrogen atom forming a benzhydryl radical. The latter may then be further oxidized to give the product, benzphenone. It is noted that the chromic acid oxidations which must involve hydrogen abstraction all show a kinetic dependence on the total chromium (VI) concentration, whereas those which are believed to proceed via an ester mechanism have a kinetic dependence on only the acid chromate ion. This difference is suggested as a possible method of distinguishing between these two mechanisms. The effect of the water content of the solvent on the rate of the reaction is discussed, and a tentative, relative, H_- scale for some of these solutions is suggested. This may permit one to determine the number of molecules of water which are involved in a reaction.

INTRODUCTION

IN recent years, there has been considerable interest in the mechanisms of the chromic acid oxidation of organic compounds. One of the most important series of reactions of this type is that which converts a saturated hydrocarbon to a carboxylic acid or a ketone. In the case of the oxidation of a methyl group, this may occur via the alcohol and the aldehyde as intermediates, and much is known about the mechanism of oxidation of these compounds. Westheimer[1] *et al.* have investigated the chromic acid oxidation of isopropyl alcohol in considerable detail, and other workers have investigated different alcohols, obtaining similar results,[2] which are that the rate law in aqueous solution is

$$v = k_a[ROH][HCrO_4^-][H^+] + k_b[ROH][HCrO_4^-][H^+]^2$$

the reaction shows a kinetic isotope effect, $k_H/k_D = 6{\cdot}6$, when the α-hydrogen is replaced by a deuterium; manganous ion reduces the rate of reaction by a factor of

* This work was presented as a part of papers given at the Reaction Mechanisms Conference, Chicago, June 1958, at the Symposium on Mechanisms of Oxidation, Queen Mary College, London, April 1959, and at the National Organic Symposium, Seattle, June 1959.

† National Science Foundation Predoctoral Fellow, 1958–59.

[1] A. Leo and F. H. Westheimer, *J. Amer. Chem. Soc.* **74**, 4383 (1952); M. Cohen and F. H. Westheimer, *Ibid.* **74**, 4387 (1952); F. Holloway, M. Cohen and F. H. Westheimer, *Ibid.* **73**, 65(1951); F. H. Westheimer and N. Nicolaides, *Ibid.* **71**, 25 (1949); W. Watanabe and F. H. Westheimer, *J. Chem. Phys.* **17**, 61(1949); F. H. Westheimer and A. Novick, *Ibid.* **11**, 506 (1943).

[2] J. Cornforth and G. Popják, *Nature, Lond.* **164**, 1053 (1949); L. Kaplan and B. Hodnett, *Abstracts of Papers presented at the 125th Meeting, Amer. Chem. Soc., Kansas City*, p. 26N American Chemical Society (1954); V. Anthony and A. C. Chatterji, *Z. Anorg. Chem.* **280**, 110 (1955); H. Kwart and P. S. Francis, *J. Amer. Chem. Soc.* **77**, 4907 (1955).

two (when the precipitated manganese dioxide is filtered off before analysis); and one manganese dioxide is formed for each two molecules of acetone formed, when manganous ion is present.

These data show that the α-hydrogen is removed in the rate determining step, and strongly suggest that the chromium species formed in this step is Cr(IV). The further observation that a chromate ester of isopropyl alcohol may be prepared, and that it decomposes readily to acetone, led to the suggestion that the ester was formed as an intermediate in the reaction. The mechanism formulated by Westheimer is

$$R_2CHOH + HCrO_4^- + H \rightleftharpoons R_2CHOCrO_3H + H_2O$$

$$R_2CHOCrO_3H + H^+ \rightleftharpoons R_2CHOCrO_3H_2^+$$

$$R_2CHOCrO_3H_2^+ + H_2O \longrightarrow R_2C{=}O + Cr(IV) + H_3O^+$$

The ester itself may also react, thus accounting for the term in the rate expression involving only one proton.

This mechanism has been attacked by Roček[3] on the grounds that the rate of reaction follows h_o in solutions containing 5–70 per cent sulphuric acid. The application of the Hammett–Zucker hypothesis[4] then suggests that a molecule of water is not involved in the rate determining step. Roček suggested the following mechanism for the

reaction. However, as pointed out by Graham and Westheimer,[5] this is not a valid criticism, for if one writes out the entire rate expression for the Westheimer mechanism and that for the Roček mechanism, including the activity coefficients, it becomes apparent that the two are identical except for a possible difference in the activity coefficients for the two activated complexes. Thus, they probably should follow the same function of acidity, regardless of which it may be. This arises because water is formed in the first equilibrium step of the ester mechanism, and the activity of water therefore appears in the denominator of the expression for the equilibrium constant. The activity of water thus introduced will cancel the activity of water which is in the rate expression as a result of the last equation.

The above data do not allow one to decide between the two possible mechanisms for the oxidation of alcohols. However, some apparently definitive data has recently been reported by Westheimer *et al.*[6] They found that the rate of oxidation of isopropyl alcohol in D_2O as the solvent was 2·4 times as fast as the reaction in water under conditions where the kinetic dependence on acid concentration was of the first order. Many examples are known of a rate enhancement of an acid catalysed reaction by changing from H_2O to D_2O.[7] This effect results from the greater acidity of D_3O^+ as compared to H_3O^+, and a consequent higher concentration of the conjugate acid of the organic substrate in the labeled solvent. The magnitude of the effect which was observed is similar to that obtained in other reactions.

If the mechanism Roček proposed were correct, an oxygen–deuterium bond

[3] J. Roček and J. Krupička, *Coll. Czech. Chem. Comm.* **23**, 2068 (1958).
[4] L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.* **61**, 2791 (1939).
[5] G. T. E. Graham and F. H. Westheimer, *J. Amer. Chem. Soc.* **80**, 3030 (1958).
[6] R. Brownell, A. Leo, Y. W. Chang and F. H. Westheimer, *J. Amer. Chem. Soc.* In press.
[7] K. B. Wiberg, *Chem. Rev.* **55**, 713 (1955).

would be broken as part of the rate determining step in the labeled solvent, leading to a normal isotope effect which would cancel the solvent isotope effect. Since this was not observed, it appears that the hydride abstraction mechanism is probably not correct. The alternate possibility, that a hydride abstraction occurs without the cleavage of the oxygen–deuterium bond, leading to the conjugate acid of acetone, is also unlikely in view of the large difference in rate of oxidation between isopropyl alcohol and diisopropyl ether.[6]

The oxidation of isopropyl alcohol has also been studied in aqueous acetic acid as the solvent[1] and here the rate law becomes

$$v = k[R_2CHOH][HCrO_4^-]h_o$$

and again a kinetic isotope effect is noted. The similarity between the reaction carried out in water and that in aqueous acetic acid make it appear probable that the mechanism is the same in the two media.

The oxidation of aromatic aldehydes in aqueous acetic acid has been examined in our laboratory[8] and the oxidation of these aldehydes in aqueous solution has also been examined.[5] The rate law in the former solvent was found to be

$$v = k[RCHO][HCrO_4^-]h_o$$

a kinetic isotope effect, $k_H/k_D = 4{\cdot}3$, was observed when the aldehyde proton was replaced by a deuterium, and the rate of reaction was found to be reduced to one-third by the addition of manganous ion. Substituted benzaldehydes which had electron releasing groups in the *p*-positions were found to be oxidized at a slower rate than benzaldehyde, and electron withdrawing groups were found to accelerate the reaction.

Since a large kinetic isotope effect was observed, the carbon–hydrogen bond must have been broken to a considerable extent in the activated complex. If the hydrogen were removed from the aldehyde as a hydride ion, considerable acylonium ion character would be developed, and in this case, electron withdrawing substituents would be expected to accelerate the reaction, whereas the opposite was observed. The following mechanism was suggested:

$$RCHO + HCrO_4^- + H^+ \rightleftharpoons RCHOCrO_3H \quad (OH)$$

$$RCHOCrO_3H \quad (OH) + H_2O \longrightarrow RCO_2H + Cr(IV) + H_3O^+$$

The mechanism is similar to that for the chromic acid oxidation of isopropyl alcohol, and it has a direct analogy with the acid catalyzed permanganate oxidation of benzaldehyde for which we have proposed a similar type of mechanism.[9] For the permanganate oxidation, the rate law was found to be

$$v = k[RCHO][MnO_4^-][HA]$$

a kinetic isotope effect was observed, and it was found that the new oxygen present

[8] K. B. Wiberg and T. Mill, *J. Amer. Chem. Soc.* **80**, 3022 (1958).
[9] K. B. Wiberg and R. Stewart, *J. Amer. Chem. Soc.* **77**, 1786 (1955).

in the product acid arose from the oxidizing agent, using O^{18} as a tracer. This required that a C–O–Mn bond be formed during the reaction, and led to the mechanism

$$RCHO + H^+ \rightleftharpoons RCHOH^+$$

$$RCHOH^+ + MnO_4^- \rightleftharpoons RCHOMnO_3 \quad (OH)$$

$$RCHOMnO_3 \,(OH) + A^- \longrightarrow RCO_2H + Mn(V) + HA$$

This mechanism accounts for general acid catalysis, the observed isotope effect, and the oxygen transfer. It might be noted that this is the only one of the above reactions in which there has been obtained direct evidence for an ester being an intermediate in the reaction which gives the product and for the necessity for the involvement of a basic species.

The value of ρ, $-0{\cdot}25$, which was observed in this reaction, is of some interest. It would be valuable to have an estimate of the magnitude of ρ for the rate determining step. Unfortunately, the effect of substituents on the hydration of benzaldehyde, which should show similar effects as the equilibrium giving the permanganate ester has not been studied. An estimate may be made on the following basis. *p*-Methoxybenzaldehyde will be stabilized by the contribution of dipolar structures involving the methoxy group:

However, this type of stabilization will not be present in the hydrate, and thus the hydration of *p*-methoxybenzaldehyde will occur to a smaller extent than that of benzaldehyde. Similarly, *p*-nitrobenzaldehyde will be hydrated to a greater extent than benzaldehyde. This type of an effect should be at least as large as that on the ionization of benzoic acids, and consequently, ρ should be at least $+1$. This conclusion is supported by the observation that in the addition of hydrogen cyanide to aromatic aldehydes, ρ was found to be 1·49.[10]

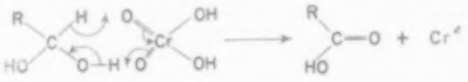
The value of ρ for the prior equilibrium, which will be assumed to be approximately unity, must be subtracted from the observed ρ to give that for the rate controlling step. The value is, then, approximately $-1{\cdot}3$, showing that a reaction in which proton abstraction occurs may still have a considerable negative ρ. There are two possible explanations for this. First, if the activated complex resembles the products, and this is reasonable in view of the large kinetic isotope effect which was observed, then the resonance stabilization of the acid by groups such as methoxy would be important in the activated complex. This would lead to a faster reaction with a methoxy substituent, and a slower reaction with a nitro substituent. Second, electron withdrawal by manganese may be the most important electronic effect in the activated complex, so that whereas the hydrogen is being removed without its pair of electrons, the carbon is still electron deficient. It is very possible that both effects are operative.

If one considers the chromic acid oxidation in the same way, the value of ρ for

[10] H. H. Jaffé, *Chem. Rev.* **53**, 191 (1953).

the rate determining step becomes approximately zero, and thus substituents have a very small effect on the rate. This again is reasonable, since a smaller kinetic isotope effect was observed here than in the permanganate oxidation (4·3 and 7·2 respectively). Thus the activated complex for the chromic acid oxidation resembles the products of the reaction to a smaller degree than that for the permanganate oxidation, and consequently the effect of substituents should be smaller.

Roček[11] has recently presented evidence which he interpreted as favoring an alternate mechanism for the oxidation of aldehydes. He found that the rates of oxidation of the hydrates of chloral, dichloroacetaldehyde, chloroacetaldehyde and of acetaldehyde increased in that order, the rates being correlated with σ^* with a ρ^* of $-1{\cdot}2$. He then suggested that it was more reasonable to propose a hydride abstraction than a proton abstraction in view of the sign of ρ^* and suggested the following mechanism



He also argued that it was the hydrate of the aromatic aldehydes which was oxidized by chromic acid, and since the ρ for the hydration equilibrium must be positive, the data which we obtained on the effect of substituents would not serve to rule out the above mechanism for these compounds also.

The discussion presented above indicates that the sign of ρ cannot be used in deciding between hydride abstraction and proton abstraction, and in view of the results obtained in the permanganate oxidation, one would expect a negative ρ for the case which was studied by Roček. Thus, his results are in accord with *either* mechanism. Roček's mechanism can be shown to be probably incorrect by comparing the rates of oxidation of acetaldehyde in water and in deuterium oxide. In the region of acid concentration which gave second order dependence on the latter, the solvent isotope effect, k_{D_2O}/k_{H_2O}, was 6·29.[12] This may be compared with the corresponding isotope effect in the oxidation of isopropyl alcohol, $k_{D_2O}/k_{H_2O} = 6{\cdot}26$.[6] As in the oxidation of isopropyl alcohol, if an oxygen–deuterium bond were cleaved in the rate determining step, as is required by Roček's mechanism, the solvent isotope effect would be reduced by a factor corresponding to the normal isotope effect for the cleavage of this bond. The observed value is, however, normal for reactions involving two protons prior to the rate determining step.[6,7] Therefore, it seems unlikely that the hydride abstraction mechanism is correct. The mechanism involving an ester intermediate will accommodate these observations, and also receives further support by the data to be presented in the discussion section on the nature of reactions which have a kinetic dependence on only the acid chromate ion.

The oxidation of hydrocarbons is considerably less well understood. Slack and Waters[13] have investigated the chromic acid oxidation of diphenylmethane in glacial acetic acid and concluded that the rate law was

$$v = k[\phi CH_2\phi][CrO_3]^2[H^+]^n$$

where the order with respect to the concentration of acid was not clearly defined.

[11] J. Roček, *Tetrahedron Letters* No. 5, 1 (1959).
[12] These experiments were performed by Dr. William Richardson, and will be reported in detail in another connection.
[13] R. Slack and W. A. Waters, *J. Chem. Soc.* 599 (1949).

The kinetic order with respect to the stoichiometric concentration of chromium trioxide was not too well established since it was based on the kinetic behavior during an experiment, rather than on the effect of chromium trioxide concentration on the rate constant.

They proposed a mechanism involving the attack of two molecules of chromic acid on the hydrocarbon in the rate controlling step to form a species having two chromium–carbon bonds, with subsequent rearrangement to a structure similar to that proposed for an Etard complex. A small amount of tetraphenylethane was obtained from the reaction, but the formation of this compound was attributed to a side reaction, rather than being an indication of a process involving free benzhydryl radicals.

The oxidation of toluene and some substituted toluenes have been investigated by Ogata *et al.*[14] They assumed a rate law corresponding to that of Slack and Waters, and observed that electron withdrawing groups retarded the reaction.

Very few aliphatic hydrocarbons have been studied. Sager and Bradley[15] found that triethylmethane was oxidized in aqueous acetic acid to give triethylcarbinol as a major initial product, which then reacted further by dehydration and oxidation of the olefin thus formed. Roček[16] has obtained similar results in the oxidation of methylcyclohexane. The rate determining step was shown by Sager and Bradley to be the abstraction of the tertiary hydrogen since a kinetic isotope effect was observed when the tertiary hydrogen was replaced by a deuterium.

These data do not, however, indicate whether the hydrogen was removed as a hydride ion or as a hydrogen atom. In the former case, a carbonium ion would be formed, which would be hydrated to form the alcohol. This would also account for the simultaneous formation of 3-pentanone since the carbonium ion would also lose a proton, giving the olefin which would in turn be rapidly oxidized to the ketone. If a hydrogen atom were removed, a tertiary free radical would be formed, which would then probably react with the oxidizing agent, either by an electron exchange reaction giving the carbonium ion, or by adding to the chromic acid to give a chromium(V) ester which could be hydrolyzed to the tertiary alcohol.

It can be seen that whereas the oxidation of alcohols and of aldehydes is fairly well understood, the oxidation of hydrocarbons requires considerable further study. The results of an investigation of one hydrocarbon, diphenylmethane, is the subject of the present work.

EXPERIMENTAL

Materials. Diphenylmethane was a commercial grade which was distilled twice giving material melting at 27°. The *p*-chloro, *m*-chloro, *p*-bromo, *m*-methoxy, *p,p'*-dimethoxy, *p*-methyl, *p,p'*-dimethyl and *p,p'*-dichlorodiphenylmethanes were prepared from the corresponding ketones by the Huang-Minlon[17] modification of the Wolff-Kishner reduction. Each of the substituted hydrocarbons was purified by chromatography over alumina followed by distillation or recrystallization.

Diphenylmethane-d_2 was prepared by the lithium aluminum deuteride reduction of dichlorodiphenylmethane.[18] To a suspension of 1 g lithium aluminum deuteride in 25 ml tetrahydrofuran maintained at reflux temp was added a solution of 6·1 g dichlorodiphenylmethane in 25 ml tetrahydrofuran over a period of 5 hr, with stirring. The solution was heated for an additional ½ hr, and then

[14] Y. Ogata, A. Fukui and S. Yuguchi, *J. Amer. Chem. Soc.* **74**, 2707 (1952).
[15] W. F. Sager and A. Bradley, *J. Amer. Chem. Soc.* **78**, 1187 (1956).
[16] J. Roček, *Coll. Czech. Chem. Comm.* **22**, 1509, 1519 (1957).
[17] Huang-Minlon, *J. Amer. Chem. Soc.* **68**, 2487 (1946).
[18] W. W. Kaeding and L. J. Andrews, *J. Amer. Chem. Soc.* **74**, 6189 (1952).

cooled and added to a mixture of ice and sulfuric acid. The organic material was taken up in ether, and the ether layer was separated and dried. Evaporation of the solvent gave 5 g yellow oil which was chromatographed over 50 g alumina, using petroleum ether for elution. Evaporation of the resultant solution and distillation gave 2·5 g diphenylmethane-d_2, b.p. 96–97° at 3 mm. The material used in the kinetic runs was repurified by chromatography, and was shown to have an insignificant amount of unlabeled and mono-deuterium labeled diphenylmethane by the absence of the methylene proton resonance bands in the NMR spectrum.

p-Methoxydiphenylmethane-d_2 was prepared by the reduction of *p*-methoxybenzophenone with lithium aluminum deuteride and aluminum chloride, using the procedure previously reported using lithium aluminum hydride.[19]

The inorganic compounds were of a reagent grade. The acetic acid was purified as described previously[8] and was diluted with water to give 95% acetic acid by weight. The 91% acetic acid is the solvent used previously.[8]

Kinetic and analytical method. The procedures used were identical with those previously reported in the study of the chromic acid oxidation of benzaldehyde.[8]

Product analysis. In several cases, the stoichiometry of the reaction was determined using product analyses. The reactions were carried out in a manner similar to the kinetic experiments (using an excess of diphenylmethane) and were allowed to proceed to completion. The reaction mixture was diluted with ice-water which had been saturated with salt, and was extracted several times with ether. The ether solution was washed with water, dried over sodium sulfate and evaporated under reduced pressure. The material thus obtained was chromatographed over alumina, the diphenylmethane being eluted with petroleum ether and the benzophenone being eluted with 1:3 ether–petroleum ether. In each case, only diphenylmethane and benzophenone were isolated. In no case was any tetraphenylethane obtained, although it was shown that it could have been isolated if it were present.

Monomer–dimer equilibrium constant in 95% acetic acid

The equilibrium constant for the reaction

$$2\ HCrO_4^- \rightleftharpoons Cr_2O_7^{2-} (+H_2O)$$

was estimated by comparing the spectra of chromium trioxide at various concentrations in 91% and 95% acetic acd. The equilibrium constant had been determined to be 25 for 91% acetic acid using the deviation from Beer's Law,[8] and it can be seen from Fig. 1 that the deviation starts at a lower concentration of chromium trioxide when 95% acetic acid is the solvent. The concentrations of chromium trioxide which give the same concentration of the dichromate ion will be given by points of equal slope for the two curves. These points are separated by 0·20 ± 0·05 log units, corresponding to a ratio of concentrations of 1·6 ± 0·2. Thus, the equilibrium constant is 65 ± 15 in 95% acetic acid.

RESULTS

The use of glacial acetic acid as the solvent for this oxidation is not desirable because of the low solubility of chromium trioxide, the difficulty in obtaining and working with pure, anhydrous acetic acid, and the lack of knowledge concerning the nature of the chromium species present in the solution. We have previously determined the acidity function, H_0, for perchloric acid in aqueous acetic acid solutions[20] and a value for the acid chromate–dichromate equilibrium constant was determined in 91 per cent acetic acid.[8] Therefore aqueous acetic acid was chosen as the solvent. The reaction proceeded at a rather low rate in 91 per cent acetic acid, and so, a 95 per cent solution was chosen for most of the kinetic experiments.

Since it appears that oxidation of the solvent may occur during the reaction,[14] the stoichiometry was examined first. The oxidation of diphenylmethane (0·036 M) with chromic acid (0·0124 M) in the presence of 0·045 M perchloric acid was effected at 30°, and the diphenylmethane and benzophenone were separated by chromatography

[19] R. F. Nystrom and C. R. A. Berger, *J. Amer. Chem. Soc.* **80**, 2896 (1958).
[20] K. B. Wiberg and R. J. Evans, *J. Amer. Chem. Soc.* **80**, 3019 (1958).

over alumina. Only 84 per cent of the theoretical amount of diphenylmethane was oxidized and 87 per cent of benzophenone, based on diphenylmethane used, was obtained. Since aromatic rings are usually not easily attacked under these conditions, it appeared that the deficiency in the amount of diphenylmethane oxidized might be attributed to the oxidation of the solvent. This oxidation could not be affected by Cr(VI) since solutions of chromic acid in this solvent are stable for long periods at the temperature used. However, oxidation by Cr(V) or (IV), which may be formed as intermediates in the oxidation, may occur.

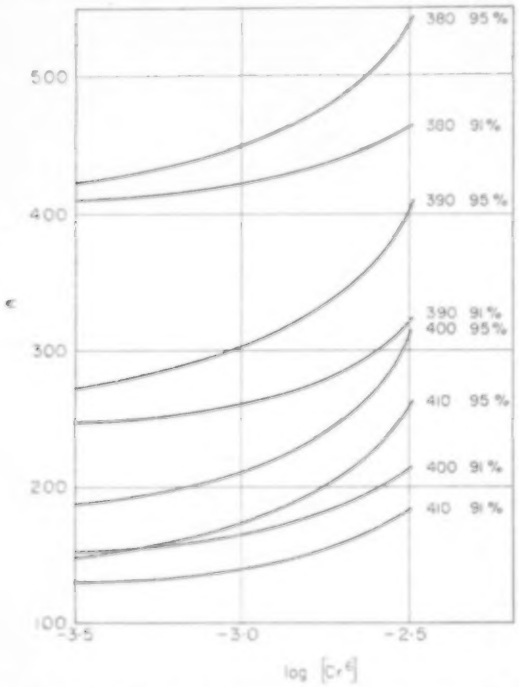


FIG. 1. Deviation from Beer's law for solutions of chromium trioxide in 91 per cent and 95 per cent acetic acid–water mixtures.

It is known that cerous ion and manganous ion react rapidly with Cr(V) and Cr(IV), whereas they react very slowly with Cr(VI).[21] The addition of cerous ion should then remove these species and should suppress the induced oxidation of the solvent. When the above experiments was repeated in the presence of 0·0038 M cerous ion, 98 per cent of the theoretical amount of diphenylmethane was used, and 86 per cent of the theoretical amount of benzophenone was isolated. A similar result was obtained when manganous ion was used. Thus, the non-stoichiometry of the reaction is largely due to induced oxidation, probably of the solvent, involving Cr(IV) or (V). In order to suppress this, all of the kinetic experiments were carried out using a considerable excess of diphenylmethane.

Oxygen is known to have an effect on chromic acid oxidations. Waters[22] has

[21] F. H. Westheimer, *Chem. Rev.* **45**, 419 (1949).
[22] W. Waters, *J. Chem. Soc.* 1151 (1946); R. Luther and T. F. Rutter, *Z. Anorg. Chem.* **54**, 1 (1907), for an example in which only inorganic reagents are involved.

noted absorption of oxygen in several cases, and in the oxidation of benzaldehyde in 91 per cent acetic acid, we have noted that the rate of disappearance of chromic acid is somewhat greater than the rate of disappearance of benzaldehyde when the reaction is carried out under nitrogen ($k_{Cr^6}/k_{\phi CHO} = 1{\cdot}1$), presumably due to a small amount of induced oxidation of the solvent, but that the reverse is true when the reaction is carried out under oxygen ($k_{Cr^6}/k_{\phi CHO} = 0{\cdot}92$). Furthermore, the rate of reaction was approximately halved in the presence of oxygen.

The effect of oxygen was therefore determined in the oxidation of diphenylmethane.

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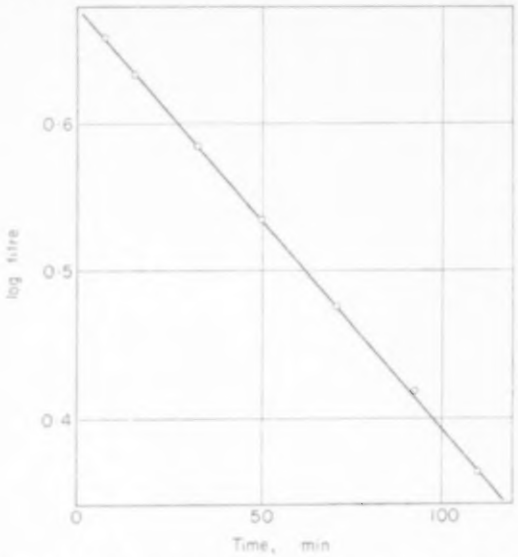


FIG. 2. Typical first order rate plot for the oxidation of diphenylamine.

The rate of reaction (followed by disappearance of chromic acid) was decreased to about 60 per cent of the value obtained in the absence of oxygen, and the effect on the rate was not significantly different when the reaction was carried out in the presence of air, or by bubbling oxygen through the solution. The stoichiometry was examined for the case in which oxygen was bubbled in, and it was found that 105 per cent of the theoretical amount of diphenylmethane was oxidized, and 90 per cent of benzophenone (based on diphenylmethane used) was obtained. All subsequent reactions were carried out in an atmosphere of nitrogen.

Each kinetic run, under these conditions, fitted a first order rate expression for the disappearance of chromic acid. A typical first order plot is given in Fig. 2. The rate of reaction as a function of the diphenylmethane concentration was determined over a 12-fold range of the latter. The second order rate constants which were calculated were constant (Table 1) indicating the reaction to be first order with respect to diphenylmethane.

The order with respect to perchloric acid was determined in the same way. A plot of log k against log $[H^+]$ gave a linear relationship with a slope of 1·27. A similar plot against H_0 gave a straight line with a slope of $-1{\cdot}05$ (Fig. 3). A consideration of the effect of the water concentration in the solvent on the rate reaction (see below)

TABLE 1. EFFECT OF DIPHENYLMETHANE CONCENTRATION OF THE RATE OF CHROMIC ACID OXIDATION

[Diphenylmethane]	$k_1 \times 10^4$ (sec^{-1})	$k_2 \times 10^4$ (l mole^{-1} sec^{-1})
0·400 M	2·35	5·87
0·250	1·38	5·52
0·200	1·05	5·25
0·150	0·833	5·55
0·100	0·617	6·17
0·050	0·269	5·38
0·030	0·175	5·83
		Ave 5·65 ± 0·26

$[HClO_4] = 0·133$ $[Cr^{6}] = ·0030$ $[NaClO_4] = 0·167$
95% acetic acid $T = 30°$

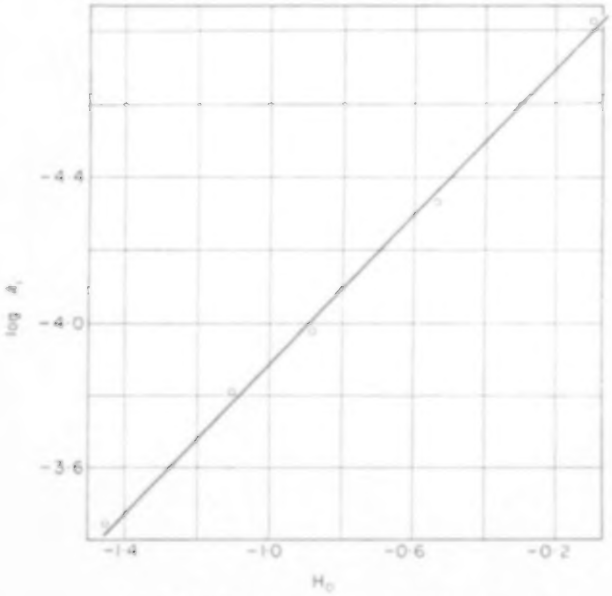


FIG. 3. Effect of acid concentration on the rate of oxidation of diphenylamine.

suggests that H_0 is a more satisfactory measure of the acidity of the medium than is the stoichiometric concentration of acid. This point has been considered previously.[8,20]

The effect of chromic acid concentration on the observed rate constants was also determined. The results are given in Tables 2 and 3. It is apparent that the rate of reaction is proportional to the total chromium (VI) concentration. It should be noted that this is not typical behavior. In the oxidation of alcohols and of aldehydes,[1,2,5,8]

the rate constants were found to decrease with increasing chromium trioxide concentration. This has been attributed to the monomerdimer equilibrium found in these solutions, only the acid chromate ion being

$$2\,HCrO_4^- \rightleftharpoons Cr_2O_7^{2-} + H_2O$$

involved in the rate expression.[1] The difference between the two cases may indicate

TABLE 2. EFFECT OF CHROMIC ACID CONCENTRATION ON ON THE OBSERVED RATE CONSTANTS IN 91% ACETIC ACID

$[Cr^6] \times 10^3$	$k_1 \times 10^4$ (sec^{-1})	$[Cr_2O_7^=]/\Sigma[Cr^6]$
36·1	3·14	0·27
30·2	3·20	0·25
22·8	3·38	0·22
15·4	3·07	0·20
7·76	2·81	0·13
3·92	2·72	0·09
1·88	3·47	0·05
0·92	3·26	0·02
0·40	3·77	0·00
	Ave 3·20 ± 0·24	

[diphenylmethane] = 0·200 $[HClO_4]$ = 0·500 T = 37°

TABLE 3. EFFECT OF CHROMIC ACID CONCENTRATION ON THE OBSERVED RATE CONSTANTS IN 95% ACETIC ACID

$[Cr^6] \times 10^3$	$k_1 \times 10^4$ (sec^{-1})	$[Cr_2O_7^=]/\Sigma[Cr^6]$
15·0	1·09	0·25
12·2	1·15	0·23
7·90	1·01	0·19
3·06	1·06	0·12
1·60	0·99	0·08
0·92	0·96	0·06
	Ave 1·04 ± ·06	

[diphenylmethane] = 0·200 $[HClO_4]$ = 0·120
$[NaClO_4]$ = 0·180 T = 30°

either that the equilibrium constant has a value such that only one of the two chromium species is present in the range of concentration used, or that both the acid chromate ion and the dichromate ion are effective, and the rate constant for the reaction of the latter is approximately twice that for the former.

The value for the equilibrium constant in 91 per cent acetic acid is available from our previous work, and an estimate of the change in value caused by going to 95 per

cent acetic acid was determined by a comparison of the spectra of solutions of chromium trioxide of various concentrations in the two solvents. This indicated a value for the equilibrium constant of 65 ± 15 for the solvent used here. This result demonstrates that only the acid chromate ion was present in the more dilute solutions which were used, and that considerable dichromate ion was present in the more concentrated solutions. Thus it appears that both species are involved in the oxidation.

At higher chromic acid concentrations than those reported in Table 1, it was

TABLE 4. EFFECT OF SUBSTITUENTS ON THE CHROMIC ACID OXIDATION OF DIPHENYLMETHANE

Substituent	k/k_H
p,p'-Dimethoxy[a]	347
p-Methoxy[a]	91·3
p,p'-Dimethyl	6·42
p-Methyl	2·28
Hydrogen	1·00
p-Chloro	0·76
p-Bromo	0·72
p,p'-Dichloro	0·49
m-Chloro	0·40
m-Bromo	0·40

$[HClO_4] = 0·240$ $[Cr_6] = 0·0030$
$[Mg(ClO_4)_2] = 0·020$ 95% acetic acid $T = 30°$

[a] In these cases, the rate of reaction increased with increasing time. The rate constants given are based on the initial slope.

found that the rate of reaction was large to begin with, and then decreased to the normal value as the reaction progressed. It is known that polychromates may be formed,[23] and solutions which contain relatively little water should be favourable for the formation of these species. If the polychromates were for some reason particularly reactive in effecting the oxidation, then the observed results would be reasonable. The reaction would proceed relatively rapidly until the concentration of chromium (VI) had dropped to a value at which relatively little polychromate would be present in equilibrium. Then the normal rate for reaction by the acid chromate and dichromate ions would be observed.

There are two possible rate determining steps for the reaction. In the first, a carbon–hydrogen bond is cleaved, and in the second, a complex is formed between the hydrocarbon and the chromium species. These may be differentiated using the kinetic isotope effect. Diphenylmethane-d_2 was prepared by the reduction of diphenyldichloromethane with lithium aluminum deuteride. The rate of reaction was found to be decreased by a factor of 6·4 ($k_2 = 10·9 \times 10^{-4}$ for the unlabeled compound, $k_2 = 1·69 \times 10^{-4}$ for the labeled material, 0·096 M R_2CH_2, 0·0030 M Cr^6, 0·240 M $HClO_4$, 0·060 M $NaClO_4$, 95 per cent acetic acid, 30°), indicating that the former is correct.

The effect of substituents was also determined, giving the data in Table 4.

[23] J. W. Mellor, *A Comprehensive Treatise on Inorganic and Theoretical Chemistry* Vol. XI, pp. 349–351.

With the exception of the *p*-methoxy substituted compounds, all of the oxidations gave good first order plots for the disappearance of chromic acid, using a considerable excess of the diphenylmethane. Since methoxy substituted aromatic compounds are oxidized by chromic acid, the methoxy substituted diphenylmethanes will be excluded from the correlations below, and will be considered separately.

A plot of the logarithm of the relative rates of reaction against the Hammett σ values[10] gave a fair fit to a straight line with a slope of −1·40. A better correlation was found in the σ^+ values of Brown and Okamoto,[24] the slope of the line being −1·17 in this case (Fig. 4).

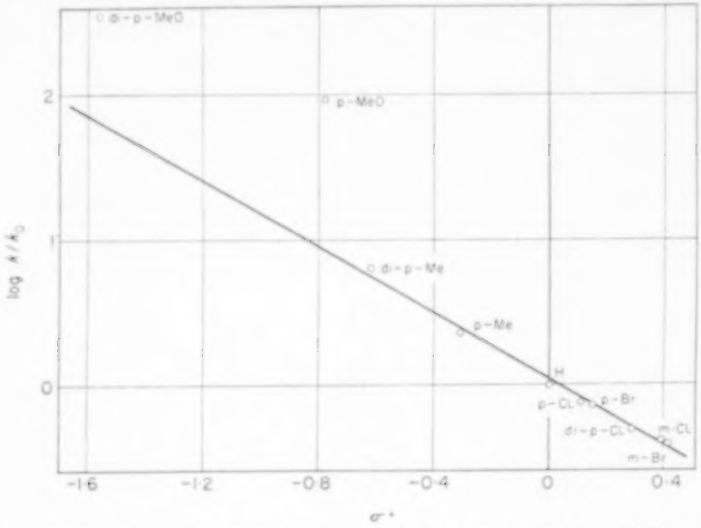


FIG. 4. Effect of substituents on the rate of the chromic acid oxidation of diphenylamine.

The water content of the solvent and the concentration of electrolyte were found to affect the rate of the chromic acid oxidation of benzaldehyde,[8] and thus data on the effect of these variables on the rate of oxidation of diphenylmethane was obtained. The results are given in Tables 5 and 6. It can be seen from the data in the former table that the dichromate ion is about twice as reactive as the acid chromate ion in all of the solutions, and that the rate of reaction of the latter is increased about 60 per cent by halving the concentration of water. It might be noted that the rate of oxidation of benzaldehyde at constant value of H_0 is independent of the water content of the medium.[8]

The enthalpy and entropy of activation were also determined. The rate constants at 20°, 30° and 40° (95 per cent acetic acid, 0·300 M $HClO_4$, 0·200 M diphenylmethane, 0·003 M Cr^6) were 1·48, 3·27 and 8·44 × 10^{-4} sec^{-1}, giving $\Delta H^{\ddagger} = 15{\cdot}2$ kcal, $\Delta S^{\ddagger} = -21{\cdot}2$ e.u.

In the studies of the oxidation of isopropyl alcohol and of benzaldehyde, an investigation of the induced oxidation of ions such as cerous and manganous during the reaction has proved helpful in defining the mechanism of the reaction. These species serve to remove the intermediate chromium species, and thereby suppress the

[24] H. C. Brown and Y. Okamoto, *J. Org. Chem.* **22**, 485 (1957); *J. Amer. Chem. Soc.* **80**, 4980 (1958).

reactions of the latter. In water as the solvent, the induced oxidation of manganous ion leads to the formation of manganese dioxide which precipitates from the solution. However, in aqueous acetic acid as the solvent, manganese dioxide does not precipitate and since the reactions carried out in the presence of manganous ion gave good first order plots for the disappearance of oxidizing power to over two half-lives, it is apparent that Mn(III) and Mn(IV) do not accumulate in the solution to an appreciable extent. The same is also true for cerous ion.

The results of this investigation are presented in Table 7. It can be seen that in all

TABLE 5. EFFECT OF WATER CONCENTRATION ON THE RATE OF THE CHROMIC ACID OXIDATION OF DIPHENYLMETHANE AT A CONSTANT VALUE OF H_0

$[Cr^6] \times 10^3$	$\%H_2O$	$[Cr_2O_7^{2-}]/\Sigma[Cr^6]$	$[HClO_4]$	$k_1 \times 10^4 sec^{-1}$
1·57	9	0·05	0·300	0·549
9·48	9	0·13	0·300	0·527
1·68	8		0·234	0·601
9·62	8		0·234	0·560
1·70	5	0·08	0·115	0·845
9·82	5	0·21	0·115	0·951
1·75	4		0·0812	0·951
9·69	4		0·0812	1·11

$H_0 = -0·84$ [diphenylmethane] = 0·200 M
$T = 30°$ ionic strength = 0·300 M

TABLE 6. EFFECT OF SALT CONCENTRATION ON THE RATE OF OXIDATION

$[NaClO_4]$	$k_1 \times 10^4$ sec^{-1}	μ
0·00	1·95	0·160
0·048	1·78	0·208
0·080	1·61	0·240
0·240	1·51	0·400

$[HClO_4]$ = 0·160 [diphenylmethane] = 0·200 $[Cr^6]$ = 0·010
$T = 30°$ 95% acetic acid

cases, there is a marked decrease in rate, to a value between three-tenths and six-tenths that observed in the absence of these ions. Any simple treatment of this phenomenon (cf. discussion) predicts a value of one-third in the absence of a chain reaction, and thus it seems reasonable to assume a limiting value of one-third for this oxidation. The same result was previously obtained in the oxidation of benzaldehyde.[8] It should be noted that the reduction in rate is affected by both the cerous (or manganous) ion concentration, and by the acid concentration. The latter appears to be the more important when manganous ion is used. The first two entries in the table which were determined using 0·120 M perchloric acid are subject to some question, since a brown

colour [possibly Mn(III)] developed on standing when the manganous ion and chromic acid solutions were mixed. The higher acid concentration repressed the formation of this colour. It is not clear how this might effect the rate constants, but it is possible that part of the reduction in rate for these two cases is due to the reaction forming the brown colour.

It was seen previously that the *p*-methoxy substituted diphenylmethanes react with chromic acid at a rate which is much greater than that for the other compounds.

TABLE 7. EFFECT OF CEROUS AND MANGANOUS ON THE RATE OF THE CHROMIC ACID OXIDATION OF DIPHENYLMETHANE

		Cerous ion				Manganous ion			
Subst.	%HOAc	$[Ce^{3}]$	$[\phi_2CH_2]$	$[H^+]$	k/k_0	$[Mn^{3}]$	$[\phi_2CH_2]$	$[H^+]$	k/k_0
H	95					0·040	0·200	0·120	0·36
	95					0·023	0·200	0·120	0·42
	95					0·020	0·200	0·180	0·47
	95					0·010	0·200	0·180	0·48
	95					0·020	0·200	0·240	0·57
*p*Cl	95					0·020	0·200	0·240	0·46
	95					0·020	0·174	0·240	0·56
H	91	0·0033	0·200	0·300	0·58	0·0067	0·200	0·300	0·58
	91	0·033	0·200	0·300	0·47	0·033	0·200	0·300	0·55
	91					0·067	0·200	0·300	0·52
	91	0·0167	0·200	0·400	0·60	0·0067	0·200	0·400	0·63
	91	0·0167	0·200	0·400	0·65	0·020	0·200	0·400	0·63
*p*Cl	91	0·033	0·151	0·300	0·44	0·0667	0·151	0·300	0·47
p,p'-diMe	91	0·0033	0·106	0·300	0·34	0·0067	0·106	0·300	0·50
	91	0·033	0·016	0·300	0·27				

$[Cr^{6}]$ = 0·0025–0·003 M

This could be due to a change in mechanism, possibly to a chain reaction, or to a change in the type of reaction. These possibilities have been examined. The stoichiometry of the oxidation of *p*-methoxydiphenylmethane was determined, and it was found that 87 per cent of the theoretical amount of the reactant was consumed and an 80 per cent yield of *p*-methoxybenzophenone based on the diphenylmethane used was obtained. The corresponding values for diphenylmethane itself were 84 per cent and 87 per cent. Thus, the site of attack is the same in both cases. The kinetic isotope effect was also determined giving $k_H/k_D = 3{\cdot}1$ ($k_0^H = 3{\cdot}66 \times 10^{-6}$ mole/l.sec.; $k_0^D = 1{\cdot}19 \times 10^{-6}$; 0·0303 M diphenylmethane, 0·060 M $HClO_4$, 0·240 M $NaClO_4$, 0·003 M Cr^6, 30°, 95 per cent acetic acid). Since we have previously shown that in any series of related reactions the kinetic isotope effect decreases as the rate of reaction increases,[25] a decrease in the isotope effect from the value observed for diphenylmethane itself (6·4) would be expected. It is clear that the rate determining step is still the cleavage of the methylene carbon–hydrogen bond.

[25] K. B. Wiberg and L. H. Slaugh, *J. Amer. Chem. Soc.* **80**, 3033 (1958).

Unlike the oxidation of diphenylmethane itself, the oxidation of the *p*-methoxy substituted derivative followed an apparent zeroth order course (Fig. 5) in the presence of excess of the latter. With *p,p'*-dimethoxydiphenylmethane, even the zeroth order plots showed an upward drift with time. This suggests that there is a small autocatalytic component in the reaction, and the effect of the initial chromium trioxide concentration on the zero order rate constants (Table 8) indicates that the reaction

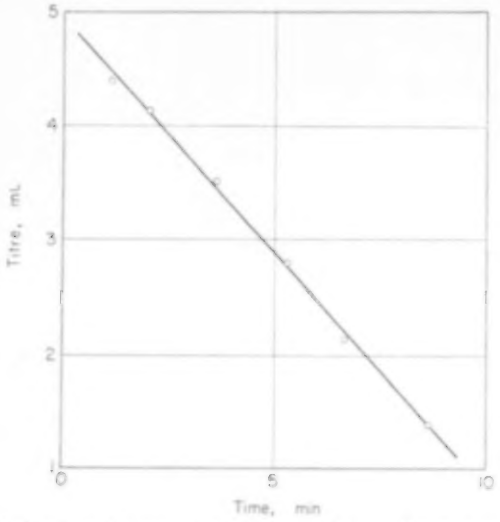


FIG. 5. Typical zero order rate plot for the oxidation of *p*-methoxydiphenylmethane.

TABLE 8. EFFECT OF THE CONCENTRATION OF THE REACTANTS ON THE RATE OF THE CHROMIC ACID OXIDATION OF *p*-METHOXYDIPHENYLMETHANE

$[Cr^6] \times 10^3$	$[R_2CH_2] \times 10^2$	$k_0 \times 10^6$ mole/l sec	$k_0/[Cr^6]$	$k_0/[R_2CH_2]$
1·74	3·33	2·29	1·31	
3·31	3·33	3·73	1·13	
6·14	3·33	6·38	1·04	
10·06	3·33	11·6	1·15	
3·31	6·67	6·92		1·04
3·31	3·33	3·73		1·12
3·33	1·33	1·40		1·05
		Ave	1·16 ± ·08	1·07 ± ·03

$[HClO_4] = 0{\cdot}060$ M $[NaClO_4] = 0{\cdot}240$ M 30° 95% acetic acid

is still first order in the oxidizing agent. The rate of the reaction was also shown to be first order with respect to the concentration of *p*-methoxydiphenylmethane (Table 8).

The effect of the acid concentration on the rate of the reaction was also determined giving the data in Table 9. A plot of log *k* against K_0 gave a straight line of slope 1·45 for the reaction carried out in 91 per cent acetic acid, and of 1·30 for the reaction

carried out in 95 per cent acetic acid. It is interesting to note that the reaction proceeded more rapidly in 91 per cent acetic acid, at a constant value of H_0, than in the 95 per cent solvent. This appears to be the first case of a chromic acid oxidation proceeding more rapidly in the more aqueous solvent.

A difference between the oxidation of *p*-methoxydiphenylmethane and other diphenylmethanes is also found in the enthalpy and enthropy of activation. The rates of reaction were determined at 20°, 30° and 40°, the rate constants being 1·21, 3·73 and 9·64 × 10^{-6} mole $l.^{-1}$ sec^{-1} (0·033 M R_2CH_2, 0·060 M $HClO_4$, 0·003 M

TABLE 9. EFFECT OF ACID CONCENTRATION AND OF SOLVENT COMPOSITION ON THE RATE OF THE CHROMIC ACID OXIDATION OF *p*-METHOXYDIPHENYLMETHANE

91% Acetic acid			95% Acetic acid		
$[HClO_4]$	H_0	$k_0 \times 10^6$	$[HClO_4]$	H_0	$k_0 \times 10^6$
0·300	−0·82	14·7	0·120	−0·86	10·3
0·200	−0·60	7·04	0·060	−0·59	3·73
0·100	−0·27	2·30	0·024	−0·14	1·17

$[Cr^6] = 0·003$ M ionic strength = 0·300 M $T = 30°$

TABLE 10. EFFECT OF MANGANOUS AND CEROUS ION ON THE CHROMIC ACID OXIDATION OF *p*-METHOXYDIPHENYLMETHANE AND *p,p'*-DIMETHOXYDIPHENYLMETHANE

Subst.	$[R_2CH_2]$	%HOAc	$[HClO_4]$	$[Ce^{3}]$	$[Mn^{2}]$	$[NaClO_4]$	$k_0 \times 10^6$	$k_{obs}/k_{uninhib}$
*p*MeO-	0·0333	95	0·120	0	0	0·180	10·3	0·
*p*MeO-	0·0333	95	0·120	0·01	0	0·120	3·56	0·35
*p*MeO	0·0333	95	0·120	0	0·004	0·168	10·1	0·98
p, p'-diMeO	0·0125	91	0·200	0	0	0·300	0·680[a]	
p, p'-diMeO	0·0125	91	0·200	0	0·0667	0·100	1·17[a]	1·72
p, p'-diMeO	0·0125	91	0·200	0	0·0333	0·200	0·866[a]	1·27
p, p'-diMeO	0·0125	91	0·200	0	0·0067	0·280	0·758[a]	1·11
p, p'-diMeO	0·0125	91	0·200	0·0333	0	0·100	0·499[a]	0·73
p, p'-diMeO	0·0125	91	0·200	0·0033	0	0·280	0·513[a]	0·75

$[Cr^6] = 0·0025$–$0·003$ M [a] Initial rates

Cr^6, 0·240 M $NaClO_4$, 95 per cent acetic acid). These values lead to $\Delta H^{\ddagger} = 17·4$ kcal, $\Delta S^{\ddagger} = -4·7$ e.u., which are quite different from those obtained in the oxidation of diphenylmethane ($\Delta H^{\ddagger} = 15·2$ kcal, $\Delta S^{\ddagger} = -21·2$ e.u.).

It is possible to determine if the reaction is a chain-process by examining the inhibition of the reaction by cerous or manganous ion. In any chain process, the intermediate chromium species Cr(V) and Cr(IV) would have to be chain carriers. Thus, a marked reduction in rate would be expected. The data which were obtained are summarized in Table 10.

It is interesting to note that with *p,p'*-dimethoxydiphenylmethane, manganous ion catalysed the reaction. This is unusual, but it has been observed previously, as in the

oxidation of lactic acid.[26] The inhibition by cerous ion was more marked with *p*-methoxydiphenylmethane than with the disubstituted compound, in the former case the rate being reduced to near the one-third ratio which might be expected. It is clear that a chain process involving the intermediate chromium species as chain carriers is ruled out by these data.

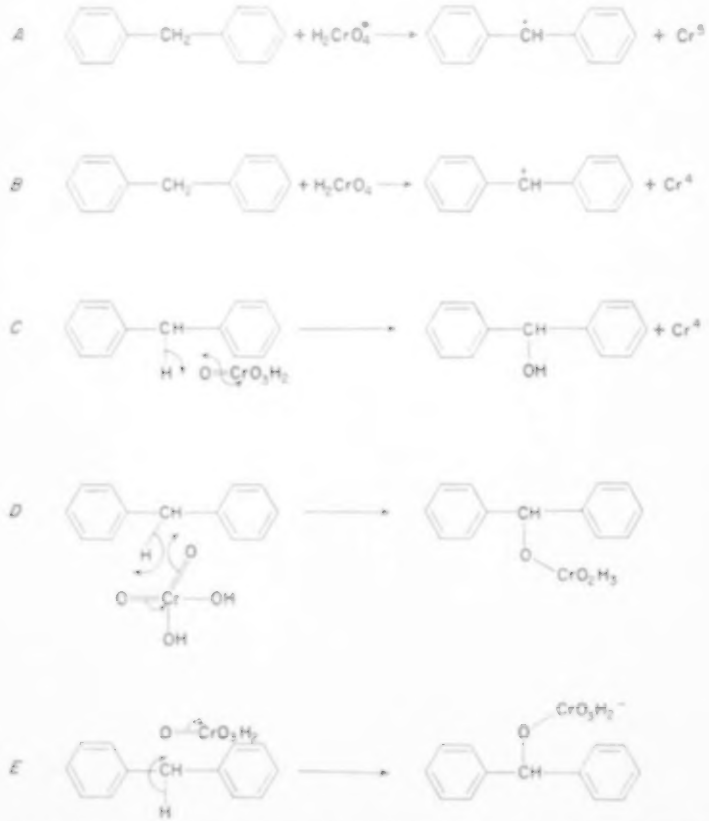
In connection with this work, the rates of reaction of a number of other hydrocarbons and their derivatives were determined. The relative rates are given in Table 11.

DISCUSSION

The observed rate law:

$$r = k[\phi CH_2\phi][CrO_3]h_0$$

suggests that the reaction may be one between diphenylmethane and a protonated species of chromium(VI). The observation of a kinetic isotope effect, $k_H/k_D = 6{\cdot}4$, indicates that the rate determining step is the cleavage of the methylene carbon-hydrogen bond. There are, then, five mechanisms by which the initial reaction may occur:



* The reactant is, for convenience, written as chromic acid, although it is clear that the acid dichromate ion is also a reactant.

[26] A. N. Dey and N. R. Dhar, *Z. Elektrochem.* **32**, 586 (1926); N. R. Dhar, *Ann. Chim.* [9], **11**, 130 (1919); *J. Chem. Soc.* **111**, 707 (1917).

In the first of these, a benzhydryl radical is formed, which may be further oxidized to benzhydrol or to the benzhydryl cation. In the other mechanisms, benzhydrol or one of its derivatives is formed directly.

It is repeatedly observed that steric effects are not important in this reaction. For example, cumene reacts faster than ethylbenzene, and the latter reacts faster than toluene. Similarly triphenylmethane reacts faster than diphenylmethane. Admittedly, this might result from a competition between a fundamental reactivity difference and a steric factor, but the universality of the observation with both aliphatic and aralkyl

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TABLE 11. RELATIVE RATES OF OXIDATION OF SOME COMPOUNDS IN 95% ACETIC ACID

Compound	Relative rate
Benzhydrol	30,000
Benzaldehyde	100
Fluorene	30
Anisole	3·4
Triphenylmethane	1·3
Diphenylmethane	1·00
Ethylbenzene	0·50
Toluene	0·16
Methylcyclohexane	0·08
t-Amylbenzene	0·054
Neopentylbenzene	0·03
Cyclohexane	0·01

hydrocarbons suggest that this is not the case. On this basis, and remembering the very large steric effects associated with nucleophilic backside displacement reactions, it seems reasonable to exclude a backside electrophilic displacement as in mechanism E.

In mechanism C, the activated complex would of necessity be non-linear. An activated complex of this type would have three normal modes of vibration, one of which would degenerate into a translational mode.* Although this mode would no longer contribute a zero-point energy difference, the other two vibrational modes would still do so. The zero-point energy difference between activated complexes containing hydrogen and these containing deuterium would in part cancel the zero-point energy difference in the ground state resulting in a low kinetic isotope effect. Since the geometry and force constants for an activated complex of this type are difficult to estimate, we make use of the suggestion of Hawthorne and Lewis[27] that reactions of this type may be considered in a first approximation to involve the conversion of a bending mode in the ground state (rather than a stretching mode) to a translation in the activated complex. Making this assumption, and using a maximum value for the pre-exponential factor in the rate expression the maximum isotope effect would be estimated to be $k_H/k_D = 3{\cdot}6$. This is actually in very good agreement

* It is probable that no one normal mode would correspond exactly to that required for leading to products. The argument still applies since one may translate the normal modes into the required ones.

[27] M. F. Hawthorne and E. S. Lewis, *J. Amer. Chem. Soc.* **80**, 4296 (1958).

with the results obtained in a number of hydrogen rearrangement reactions in which the activated complex must of necessity be non-linear (Table 12).

Since the observed kinetic isotope effect (6·4) is in the range of the maximum values which are experimentally observed, it would appear that mechanism C may be eliminated from consideration. Mechanism D may also fall in this category for the same reason, but because of the larger ring which is involved, there are as yet no good analogies. A better argument against mechanism D is that models suggest that

TABLE 12. KINETIC ISOTOPE EFFECTS FOR HYDROGEN REARRANGEMENT REACTIONS

Reactions	k_H/k_D	Ref.
$\Phi_2C(HO)-CH(OH)\Phi + H^+ \rightarrow \Phi_2CH-C(=O)\Phi$	3·3	28
$(CH_3)_2C(HO)-CH(OH)CH_3 + H^+ \rightarrow (CH_3)_2CH-C(=O)CH_3$	1·8	29
$(CH_3)_2CH-CH(OTs)CH_3 \rightarrow (CH_3)_2C(OAc)-CH_2CH_3$	2·1	30
$\Phi CHO\dagger + HO^- \rightarrow \Phi CH_2OH + \Phi CO_2^-$	1·8	31

† This assumes that the mechanism involves the addition of $\Phi CH(OH)O^-$ to ΦCHO followed by rate controlling intramolecular hydrogen migration.

considerable steric effects should be associated with the activated complex for this type of reaction. Again, since these appear to be absent, this mechanism is probably also incorrect.

This then leaves only mechanisms A and B to be considered. The effect of substituents may be used as an aid in differentiating between them. Mechanisms which involve the formation of an electron deficient carbon adjacent to an aromatic ring usually give a value of ρ^+ between -3 and -5.[24] For example, the solvolysis of benzhydryl chloride gave a ρ^+ of $-4{\cdot}05$.[32] Hydrogen atom abstractions from toluene on the other hand normally give values of ρ between $-0{\cdot}75$ and $-1{\cdot}5$.[19] The value of ρ^+ obtained in the present reaction was $-1{\cdot}17$, in good agreement with that for the latter type of reaction. It might be noted that in general hydrogen atom abstractions as well as reactions leading to carbonium ions are better correlated with σ^+ than with σ, and the reasons for this have been discussed by Russell.[33]

[28] C. J. Collins, W. T. Rainey, W. B. Smith and I. A. Kaye, *J. Amer. Chem. Soc.* **81**, 460 (1959).
[29] W. B. Smith, R. E. Bowman and T. J. Kmet, *J. Amer. Chem. Soc.* **81**, 997 (1959).
[30] S. Winstein and J. Takahashi, *Tetrahedron* **2**, 316 (1958).
[31] K. B. Wiberg, *J. Amer. Chem. Soc.* **76**, 5371 (1954); C. G. Swain and W. A. Sheppard, *Abstract of papers presented at the 127th Nat. Meeting of the Amer. Chem. Soc., Cincinnati*, p. 40 N. American Chemical Society (1955).
[32] J. F. Norris and C. Banta, *J. Amer. Chem. Soc.* **50**, 1804 (1928); J. F. Norris and J. T. Blake, *Ibid.* **50**, 1808 (1928).
[33] G. A. Russell, *J. Org. Chem.* **23**, 1407 (1958).

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Further evidence in support of mechanism A may be found in a comparison of the rates of hydrogen abstraction from toluene, ethylbenzene, diphenylmethane and triphenylmethane, and the rates of solvolysis of the corresponding chlorides (Table 13). It can be seen that there is good agreement between the rates of oxidation and the rates of hydrogen atom removal, but that the range of rates of solvolysis is larger by many orders of magnitude. It seems fairly clear then, that the initial reaction involves the abstraction on a hydrogen with one electron giving a benzhydryl radical as the first intermediate.

TABLE 13. RELATIVE RATES OF OXIDATION, HYDROGEN ABSTRACTION AND SOLVOLYSIS

Compound	Rel. rate of oxidation	Rel. rate[34] of H abst. by Cl_3C.	Rel. rate[35] of solvolysis of chlorides
Toluene	1·0	1·0	1·0
Ethylbenzene	3·1	3·0	100
Diphenylmethane	6·3	8·0	2000
Triphenylmethane	8·1	16·7	10^7

This is presumably the case with triphenylmethane and toluene also. It is interesting to note that a value of ρ^+ of $-1{\cdot}12$ may be calculated from the effect of substituents on the rate of oxidation of toluene.[14] This is very close to the value obtained in the present work.

There are several possible ways in which the benzhydryl radical may react further. First, there is a possibility of combination with the chromium(V) before the two species diffuse away from each other. Second, the radical may react with chromium (VI) either by an electron transfer process to give the benzhydryl cation and chromium (V), or by addition, giving an ester of chromium (V) which may decompose directly to benzophenone and chromium (III). It is not possible to distinguish between these possibilities by simple kinetic experiments alone. Therefore a detailed discussion of this feature of the reaction will be postponed until further experimental work has been completed.

The unusual reactivity of the *p*-methoxy substituted compounds must now be considered. The data which are available exclude a chain process. Thus one is led to the conclusion that the reaction which occurs in this case is probably one in which greater electron deficiency is found at the site of the reaction than with the other diphenylmethane derivatives. The *p*-methoxy group is unusually well able to stabilize an electron deficiency.[36] The data also support the assumption of a change in mechanism for the reaction of this compound. For example, the effect of water concentration in the solvent, and the value of the entropy of activation were markedly different than for diphenylmethane. One of the simplest rationalizations is that the process involves hydride abstraction with the methoxy substituted derivative, leading to the benzhydryl cation. However, it is difficult to present definitive evidence for any particular mechanism based on the little data which are now available.

[34] E. C. Kooyman, *Rec. Trav. Chim.* **69**, 492 (1950).
[35] A. Streitwieser, Jr., *Chem. Rev.* **56**, 571 (1956).
[36] N. C. Deno and A. Schriesheim, *J. Amer. Chem. Soc.* **77**, 3051 (1955).

It might be noted that there are several examples of reactions in which the introduction of a *p*-methoxy group caused the mechanism to change from a free radical type to one involving a carbonium ion. For example, Criegee *et al.*[37] examined the reaction of styrene and *p*-methoxystyrene with lead tetrabenzoate in benzene solution. The former gave the normal product of a free radical type reaction, phenyl-1, 2-ethanediol benzoate, whereas the latter gave a product, 2-*p*-methoxyphenyl-1, ethanediol dibenzoate, which almost certainly arose via the formation of a cationic species.

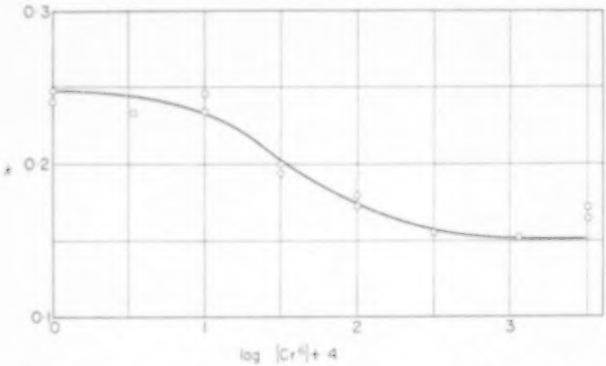

FIG. 6. Effect of chromium (VI) concentration on the rate of oxidation of di-isopropyl ether. The data are taken from ref. 6.

Finally, there are two aspects of the reaction which deserve special comment. These are the kinetic dependence on total chromium (VI) concentration, and the effect of the water concentration of the solvent on the rate of reaction. As was mentioned previously, the oxidations of alcohols and of aldehydes, both of which are believed to proceed via an ester mechanism, have a kinetic dependence on only the acid chromate ion, whereas in the present case, it is apparent that both the acid chromate ion and the dichromate ion must be reactive. The latter is also true for the oxidation of methylcyclohexane,[16] and of diisopropyl ether[6] (Fig. 6). In the latter three cases hydrogen abstraction must occur directly by means of the oxidizing agent. However, in the reactions of aldehydes and of alcohols, a likely path for the formation of the intermediate ester is

$$ROH + HCr_2O_7^- \longrightarrow ROCrO_3^- + HCrO_4^- + H^+$$

Thus the rate law for the overall reaction would be

$$r = \frac{k[ROH][Cr_2O_7^-][H^+]}{[HCrO_4^-]} = k'[ROH][HCrO_4^-][H^+]$$

The formation of the ester may then actually involve the dichromate ion, resulting in a kinetic dependence on only the acid chromate ion. It is proposed that this difference in rate law between the two types of reactions may serve to differentiate between the reactions involving an ester intermediate, and those involving direct hydrogen abstraction.

It has also been noted that the rates of oxidation of hydrocarbons and of alcohols

[37] R. Criegee, P. Dimroth, K. Noll, R. Simon and C. Weis, *Chem. Ber.* **90**, 1070 (1957).

by chromic acid are strongly accelerated by decreasing the water content of the medium,[2,16] whereas, at a constant value of the acidity function, H_0, the rate of oxidation of benzaldehyde was unaffected by the water content.[8] The data which are presently available are not sufficiently complete to make a detailed analysis, but at a constant value of H_0, it appears that the oxidation of alcohols and of hydrocarbons is subject to an approximate first order retardation by water. The reason for this is not difficult to see. The H_0 acidity function is defined for the reaction

$$H^+ + B \rightleftharpoons BH^+$$

whereas the reaction in question is of the type

$$H^+ + A^- \rightleftharpoons HA$$

which requires the acidity function H_-. Unfortunately, values for this acidity function in the medium used are not available, but an estimate of the difference between H_0 and H_- may be made. We have previously noted that a plot of $H_0 - \log [H^+]$ against $\log M_{H_2O}$ for dilute perchloric acid solutions in aqueous acetic acid mixtures gave a straight line from 25–95 per cent acetic acid, having a slope of 2.[20] Since the net charge is not changed in the reaction, this slope may be roughly equated with the change in the number of water of hydration in the reaction

$$H^+ \cdot nH_2O + B \rightleftharpoons BH^+ \cdot (n-2)H_2O + 2H_2O$$

In the reaction of an anion with a solvated proton, a larger number of water molecules of hydration will be liberated, since the conjugate acid, HA, will be relatively non-solvated. If the number of water of hydration of BH^+ in these solutions is one (i.e. n above equals 3) then the difference between H_0 and H_- will be roughly $\log M_{H_2O}$ (remembering however, that H_- will be more strongly affected by a change in dielectric constant than will H_0). Thus in the absence of other better data, it is suggested that the effect of water on the rate of oxidation of alcohols and of hydrocarbons may be used as a rough measure of the change in H_- with water concentration.

These suggestions are in good accord with the data we have obtained on the oxidation of benzaldehyde with chromic acid. It was assumed that a water molecule is required for the abstraction of a proton from the intermediate ester. Here, the rate expression will contain the concentration of water, and instead of obtaining first order retardation by water, the latter now has no effect. This illustrates the use of this rough H_- scale to determine the number of water molecules associated with the activated complex. In connection with the alcohol oxidation it must be remembered that although a water molecule is required for the decomposition of the intermediate ester, one water molecule is formed in the prior equilibrium, and so the net number of water molecules involved is zero.

Acknowledgement—We wish to thank the National Science Foundation for a grant which helped support this work.

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SYSTEMATIK UND NOMENKLATUR DER FLAVONOIDE

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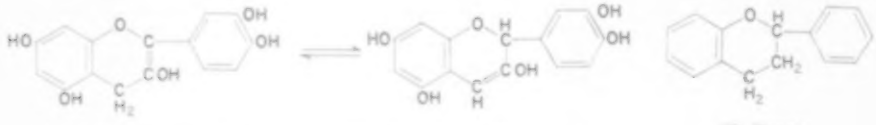
I

DER bisher übliche Sammelname "Leuko-anthocyanidine" wurde von Rosenheim[1] eingeführt und von Robinson und Robinson[2] trotz gewisser Bedenken weiter verwendet. Er diente für die von Tswett[4] beschriebenen farblosen Flavonoide und Hydroxy-chalkone, die samt ihren Glykosiden, Säureestern, Polymerisationsprodukten etc., mit Mineralsäuren Anthocyanidine liefern. Der Sammelname Leuko-anthocyanidine für diese Vielzahl von Substanzen ist heute unzweckmässig geworden, seit die Chemie der Hydroxyflavane und -flavene Fortschritte gemacht hat. Denn nach den bewährten Regeln der Farbstoffchemie können beispielsweise in der Reihe des Cyanidins nur zwei—wahrscheinlich tautomere—Verbindungen als Leuko-cyanidin bezeichnet werden, das 5,7,3′,4′-Tetrahydroxy-flaven-2-ol-3 (I) und das 5,7,3′,4′-Tetrahydroxy-flaven-3-ol-3 (II).



I. 5.7.3'.4' – Tetrahydroxy–flaven – 2 – ol – 3 Cyaniden – 2 – ol – 3 3)

II. 5.7.3'.4' – Tetrahydroxy–flaven – 3 – ol – 3 Cyaniden – 3 – ol – 3 3)

V. Flavan

Infolgedessen haben Freudenberg und Weinges[5] als Sammelnamen für sämtliche mit Mineralsäure Anthocyanidin liefernde Substanzen den Namen Pro-anthocyanidine vorgeschlagen und damit die ausdrückliche Zustimmung von R. Robinson (Privatmitteilung) gefunden.

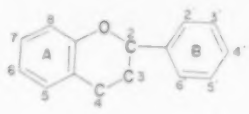
II

Für die Benennung der Catechine haben vor bald 25 Jahren Freudenberg *et al.*[6] die Bezeichnung Anthocyanidole vorgeschlagen und die Benennung im einzelnen an das zugehörige Anthocyanidin angelehnt. Das gewöhnliche Catechin (VIII) sollte danach Cyanidol genannt werden. Einer Anregung von R. Kuhn folgend schlagen wir, auf diesem Wege weitergehend, nunmehr eine neue Ordnung für die Bezeichnung der Flavonoide vor. Die Nomenklatur schliesst sich äusserlich an die im Jahre 1957

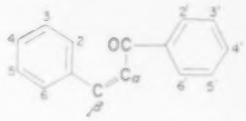
[1] O. Rosenheim, *Biochem. J.* **14**, 178 (1920).
[2] G. M. Robinson und R. Robinson, *Biochem. J.* **27**, 206 (1933).
[3] Hier ist die unten vorgeschlagene Bezeichnung verwendet.
[4] M. Tswett, *Biochem. Z.* **58**, 225 (1914); *Ber. Dtsch. Bot. Ges.* **32**, 61 (1914); vergl. P. Robinson, *J. Chem. Educ.* **36**, 144 (1959).
[5] K. Freudenberg und K. Weinges, *Fortschritte d. Chemie org. Naturstoffe*, Wien XVI, 1 (1958).
[6] K. Freudenberg, Karimullah und G. Steinbrunn, *Liebigs Ann.* **518**, 37 (1935).

festgesetzte Nomenklatur der Steroide[7] an. Im einzelnen Punkten weichen wir bewusst von den Grundsätzen der strengen Nomenklatur ab, weil die gewünschte Vereinfachung nur so zu erreichen ist. Die Vorschläge lauten im einzelnen:

1. Die Flavonoide werden wie bisher nach Formel III beziffert. Dass die entsprechenden Chalkone und Hydrochalkone[8] anders beziffert werden (IV), sei hier erwähnt.

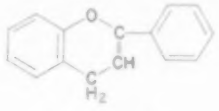


III

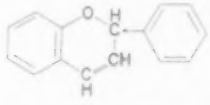


IV

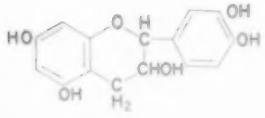
2. Die *systematische* Bezeichnung geht auf das Flavan V oder das Flaven-2 VI oder Flaven-3 VII zurück. In der Bezeichnung werden die *phenolischen* Hydroxyle vorangestellt. Catechin (VIII) ist 5,7,3′,4′-Tetrahydroxy-flavanol-3. Quercetin (IX) ist 5,7,3′,4′-Tetrahydroxy-flaven-2-ol-3-on-4. Leuko-cyanidin (I) ist 5,7,3′,4′-Tetrahydroxy-flaven-2-ol-3, Leuko-cyanidin (II) ist 5,7,3′,4′-Tetrahydroxy-flaven- 3-ol-3, usw. Diese Bezeichnungen sind zwar eindeutig, aber nicht einprägsam und schwer auszusprechen. Deshalb wird im folgenden eine Bezeichnung vorgeschlagen, die an gebräuchliche Namen angelehnt ist.



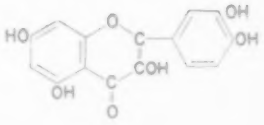
VI Flaven – 2



VII Flaven – 3



VIII Catechin und Epicatechin
5.7.3'.4' – Tetrahydroxy – flavanol – 3
Cyanidanol – 3 3)



IX Quercetin
5.7.3'.4' – Tetrahydroxy – flaven – 2 – ol – 3 – on – 4
5.7.3'.4' – Tetrahydroxy – flavenolon
Cyanidenolon 3)

3. *Einteilung*. Die Flavonoide werden nach der Stellung der phenolischen Hydroxyle in Reihen eingeteilt. Jede Reihe wird durch 2 Zahlen bezeichnet, deren erste die Anzahl der Hydroxyle im Ring A (in den Formeln links geschrieben) bedeutet, die zweite die Zahl der Hydroxyle im Ring B. Die Zählung beginnt mit dem Flavan 0 : 0; Cyanidin mit 2 Hydroxylen in jedem Ring gehört beispielweise der Reihe 2 : 2 an. Jede Reihe, zum Beispiel 2 : 2, enthält mehrere Gruppen, von denen die des Cyanidans[3] eine ist. Die Reihenfolge beginnt mit den niedersten Ziffern. Die erste Gruppe

[7] *Nomenclature of Organic Chemistry* S.71. Butterworths, London (1957).
[8] *Beilstein* 4. Aufl., VII, E. II, 380 und 423.

der Reihe 2 : 2 wäre 5, 6, 2′, 3′-Tetrahydroxy-flavan. Da diese Gruppe keinen natürlichen Vertreter aufweist, ist sie hier nicht angeführt und auch mit keinem Namen versehen worden.

4. *Gebrauchsnamen.* Die Stammsubstanz aller Flavonoide ist das Flavan. Es enthält am Kohlenstoffatom 2 ein Wasserstoffatom, an Kohlenstoffatomen 3 und 4 je zwei. Diese Gruppierung im Heterocyclus wird wie ein Kohlenwasserstoff behandelt; ausserdem werden die Namen von 6 Grundtypen gebildet, die sich durch die Zahl und die Stellung der phenolischen Hydroxyle unterscheiden. Die 6 Grundtypen repräsentieren jene Gruppen, die in der Natur bisher die meisten Vertreter gestellt haben. Die Bezeichnung dieser Grundtypen ist an einen markanten Vertreter der betreffenden Gruppe angelehnt. Allesamt erhalten sie die Endsilben -idan. Dies dient dazu, die Zugehörigkeit zu den Flavonoiden in Texten und Registern hervorzuheben. In der ersten Spalte der folgenden Übersicht ist der Name der Grundtype, also des betreffenden Hydroxyflavans, angeführt. In der zweiten Spalte ist die systematische Bezeichnung wiedergegeben. In der dritten Spalte ist jene Verbindung aus der betreffenden Gruppe verzeichnet, die zur Namenbildung gedient hat.

TABELLE

Fisidan	7,3′,4′-Trihydroxy-flavan	Fisetin
Robidan	7,3′,4′,5′-Tetrahydroxy-flavan	Robinetin
Chrysidan	5,7-Dihydroxy-flavan	Chrysin
Pelargidan	5,7,4′-Trihydroxy-flavan	Pelargonidin
Cyanidan	5,7,3′,4′-Tetrahydroxy-flavan	Cyanidin
Delphidan	5,7,3′,4′,5′-Pentahydroxy-flavan	Delphinidin

Alle übrigen Flavonoide sind nach dem Flavan oder einer dieser 6 Grundtypen benannt.

Bei Dihydroxy-flavanen wird auf einen Gebrauchsnamen verzichtet, da bei einer solchen Substanz, z.B. dem 7,4′-Dihydroxy-flavan, die systematische Bezeichnung ohne weiteres vom Leser oder Hörer aufgenommen werden kann. Einzig das 5,7-Dihydroxy-flavan hat wegen der Häufigkeit dieser Gruppierung einen Grundtypennamen, nämlich Chrysidan, erhalten. Bei Gruppen, die nur wenige Vertreter haben, wie z.B. 5,8,3′,4′-Tetrahydroxy-flavan, wird gleichfalls der systematische Name beibehalten und auf einen Gebrauchs-namen verzichtet. Alle übrigen Gruppenbezeichnungen werden auf eine der 6 oben angeführten Grundtypen bezogen. Das 6,7,3′,4′-Tetrahydroxy-flavan wird beispielsweise 6-Hydroxy-fisidan genannt. Diese Bezeichnung hat zugleich den Vorteil, dass das ungewöhnliche Vorkommen eines 6-Hydroxyls zum Ausdruck gebracht wird. Kernmethylierte Flavonoide werden nach dem Stammkörper bezeichnet, z.B. 6-Methyl-5,7-dihydroxy-flavan wird 6-Methyl-chrysidan.

Von den Grundtypen aus lassen sich sämtliche Namen der gesättigten und ungesättigten Alkohole und Ketone ableiten. Quercetin z.B., dessen gut eingebürgerter Name keineswegs abgeschafft werden soll, heisst in dieser Bezeichnungsweise Cyanidenolon . Einzig die Flavyliumsalze bedürfen einer besonderen Festsetzung. Wenn der Heterocyclus kein Hydroxyl trägt, wie im Luteolinidin (Gruppe 2 : 2), wird die Endsilbe "an" in "ylin" verwandelt. Für dieses Flavyliumsalz ergibt sich also Cyanidylin, während die zugehörige 3-Hydroxylverbindung die Endsilbe -in erhält. Cyanidin

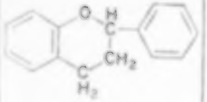
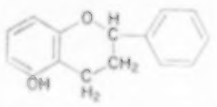
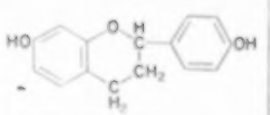
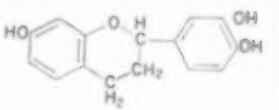
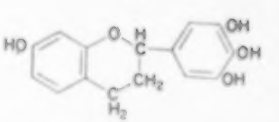
behält somit seinen alten Namen. Aus Flavan wird Flavylin und—ungeachtet der obigen Bestimmung—für die 3-Hydroxyl-flavylium-verbindung der Name Flavidin gebildet.

5. Der Name der Methyläther wird aus dem Namen der Gruppe gebildet, ebenso der Name der Methylendioxy-Verbindungen, die Methylenäther genannt werden. Von kernsubstituierten Flavonoiden sind in der folgenden Aufstellung nur die Methylverbindungen angeführt, z.B. 6-Methyl-cyanidan. In einem Fall ist auch eine Carbonsäure erwähnt. Die Glykoside sind nicht angeführt. Sie sollten, wo es irgend möglich ist, nach dem Aglykon benannt werden. Weitere Namen sollten nicht mehr erfunden werden.

6. In dem vorliegenden Vorschlag sind im ganzen 6 neue Namen von Grundtypen eingeführt worden. Dafür sind ohne die sehr zahlreichen Glykoside und sonstigen Derivate mehr als 180 Namen vom Standpunkt der chemischen Systematik ersetzbar.

7. Für die Aufstellung der folgenden Liste hat das Buch von W. Karrer, *Konstitution und Vorkommen der organischen Pflanzenstoffe* (exklusive Alkaloide)[9] gedient. Die vierstelligen Ziffern, die bei den einzelnen Substanzen angeführt werden, sind die Numerierungen in dem genannten Buch. Die Liste wurde ergänzt durch ein Verzeichnis von T. R. Seshadri[10]. Den Substanzen, die dieser Quelle entnommen sind, wurde "Sesh" und die Seitenzahl beigefügt. Angaben aus einer Arbeit von Venkataraman[11] sind mit "Venk." bezeichnet. Substanzen, die mit diesen Kennzeichen versehen sind, sind Naturstoffe. Einige seither bekannt gewordene natürliche Flavonoide sind eingefügt und mit Zitaten versehen worden. Die zur Zeit gebräuchlichen Namen sind eingeklammert. Die Liste erhebt keinen Anspruch auf Vollständigkeit. Die Substanzen sind innerhalb der Reihen numeriert, um die Zitierung nach dieser Abhandlung zu erleichtern; Cyanidin ist z.B. 2 : 2/(19). Das Verzeichnis auf S. 349 enthält die Trivialnamen der Flavonoide.

[9] Birkhäuser Verlag Basel und Stuttgart 1958.
[10] T. R. Seshadri, *Tetrahedron* **6**, 159 (1959).
[11] K. Venkataraman in Zechmeisters, *Fortschr. Chem. Org. Naturstoffe* **17**, 1 (1959).

	0:0 	1:0 	1:1 	1:2 	1:3 
1	(1) Flavan	(1) 5-Hydroxyflavan	(1) 7,4′-Dihydroxyflavan	7,3′,4′-Trihydroxyflavan. (1) Fisidan	7,3′,4′,5′-Tetrahydroxyflavan (1) Robidan
2	(2) Flavanol-3			(2) Fisidanol 1761[3] (Fisetinidol, Quebrachocatechin)	(2) Robidanol (Robinetinidol)[4]
3	Flavandiol-3,4 (3) Flavandiol		(2) 7,4′-Dihydroxyflavandiol (Guibourtacacidin)[1]	(3) Fisidandiol (Leukofisetinidin-hydrat, Leuko-fisetinidin, Mollisacacidin)[3]	(3) Robidandiol (Leukorobinetinidin-hydrat)[5]
4	Flavanon-4 (4) Flavanon		(3) 7,4′-Dihydroxyflavanon 1600 (Liquiritigenin)	(4) Fisidanon 1621 (Butin)	
5	(5) Flavylin			(5) Fisidylin (Butinidin)[1]	
6	(6) Flavidin		(4) 7,4′-Dihydroxyflavidin, Stammkörper des Nudicaulins 1756	(6) Fisidin (Fisetinidin)[2]	(4) Robidin (Robinetinidin)[5]
7	Flaven-2-on-4 (7) Flavenon 1435 (Flavon)	(2) 5-Hydroxyflavenon 1436 (5-Hydroxyflavon Primuletin, Venk.)	(5) 7,4′-Dihydroxyflavenon (6) 7,4′-Dihydroxyflavenon-4′-methyläther 1448 (Pratol)		
8	Flavanol-3-on-4 (8) Flavanolon			(7) Fisidanolon 1636 (Fustin)	(5) Robidanolon 1639 (Dihydrorobinetin)
9	Flaven-2-ol-3-on-4 (9) Flavenolon (Flavonol)			(8) Fisidenolon 1521 (Fisetin) (9) Fisidenolon-3,7-dimethyl-3′,4′-methylenäther 1574a (Desmethoxy-kanugin)	(6) Robidenolon 1573 (Robinetin) (7) Robidenolon-3,7,3′-trimethyl-4′,5′-methylenäther 1574 (Kanugin)

[1] Naturstoff; D. G. Roux, *Nature, Lond.* **183,** 890 (1959). [2] Bisher nur synthetisch gewonnen. [3] Naturstoff; H. H. Keppler, *J. Chem. Soc.* 2721 (1957); Naturstoff; Synthese: D. G. Roux u. K. Freudenberg, *Liebigs Ann.* **613,** 56 (1958). [4] Naturstoff; D. G. Roux, *Nature, Lond.* **182,** 1798 (1958). [5] Naturstoff; K. Weinges, *Liebigs Ann.* **615,** 203 (1958).

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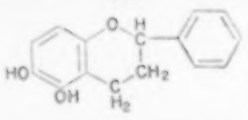
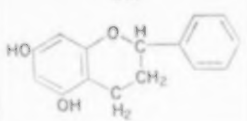
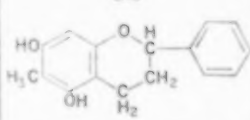
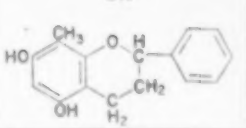
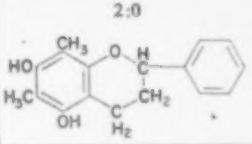
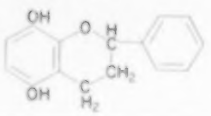
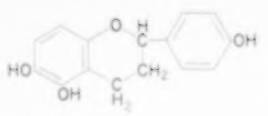
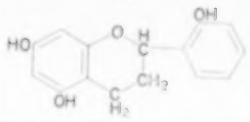
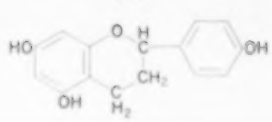
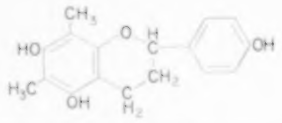
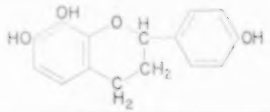
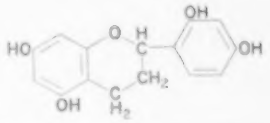
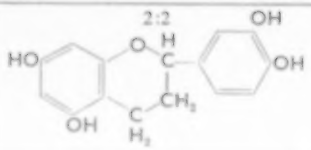
	2:0 	2:0 	2:0 	2:0 	2:0 
1	5,6-Dihydroxy-flavan (1)	5,7-Dihydroxy-flavan (3) Chrysidan	6-Methyl-5,7-dihydroxy-flavan. (14) 6-Methylchrysidan	8-Methyl-5,7-dihydroxy-flavan. (17) 8-Methylchrysidan	6,8-Dimethyl-5,7-dihydroxy-flavan. (19) 6,8-Dimethylchrysidan
2					
3					
4		(4) Chrysidanon 1594 (Pinocembrin) (5) Chrysidanon-5-methyl-äther 1595 (Alpinetin) (6) Chrysidanon-7-methyl-äther 1596 (Pinostrobin)	(15) 6-Methyl-chrysidanon 1597 (Cryptostrobin). vgl. Sesh. 198.	(18) 8-Methyl-chrysidanon 1598 (Strobopinin) vgl. Sesh. 198	(20) 6,8-Dimethyl-chrysidanon 1599. (Desmethoxy-matteucinol)
5					
6					
7	(2) 5,6-Dihydroxy-flavenon-dimethyläther 1436a (5,6-Dimethoxyflavon)	(7) Chrysidenon 1438 (Chrysin) (8) Chrysidenon-7-methyl-äther 1441 (Tectochrysin)	(16) 6-Methyl-chrysidenon 1447 (Strobochrysin).		
8		(9) Chrysidanolon 1633 (Pinobanksin) (10) Chrysidanolon-7-methyläther 1634, 1634a (Alpinon)	16(a) 6-Methyl-chrysidanolon-7-methyläther (Strobobanksin) Sesh. 194.		
9		(11) Chrysidenolon 1490 (Galangin) (12) Chrysidenolon-3-methyläther 1491 (Galangin-3-methyläther) (13) Chrysidenolon-7-methyläther 1492 (Izalpinin)			

	2:0 	2:1 	2:1 	2:1 
1	(21) 5,8-Dihydroxy-flavan	(1) 5,6,4′-oder 5,8,4′-Trihydroxy-flavan	5,7,2′-Trihydroxy-flavan (3) 2′-Hydroxychrysidan	5,7,4′-Trihydroxy-flavan (7) Pelargidan
2				(8) Pelargidanol 1760 (Afzelechin) (9) Pelargidanol-3-methyläther[1] (Aranachidose)
3				(10) Pelargidandiol[2] (Leuko-pelargonidin)
4			(4) 2′-Hydroxy-chrysidanon-2′-methyläther 1619 (Citronetin)	(11) Pelargidanon 1602 (Naringenin) (12) Pelargidanon-7-methyläther 1606 (Sakuranetin) (13) Pelargidanon-4′-methyläther 1609, 1612 (Isosakuranetin, Citrifoliol)
5				(14) Pelargidylin 1702 (Apigenidin)
6				(15) Pelargidin 1705 (Pelargonidin)
7	(22) 5,8-Dihydroxy-flavenon 1437 (Primetin)			(16) Pelargidenon 1449 (Apigenin) (17) Pelargidenon-7-methyläther 1456 (Genkwanin) (18) Pelargidenon-4′-methyläther 1458 (Acacetin) (19) Pelargidenon-7,4′-dimethyläther 1462
8				(20) Pelargidanolon 1635 (Aromadendrin) (21) Pelargidanolon-7-methyläther, Sesh. 198 (Aromadendrin-7-methyläther)
9		(2) 5,6,4′-oder 5,8,4′-Trihydroxy-flavenolon 1513 (Pratoletin)	(5) 2′-Hydroxy-chrysidenolon 1493 (Datiscetin) (6) 2′-Hydroxy-chrysidenolon-2′-methyläther 1495 (Ptaero-xylol)	(22) Pelargidenolon 1497 (Kämpferol) (23) Pelargidenolon-7-methyläther 1511 (Rhamnocitrin) (24) Pelargidenolon-4′-methyläther 1512[3] (Kämpferid)

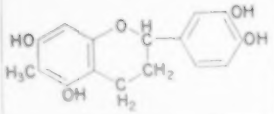
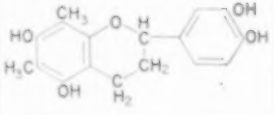
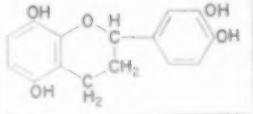
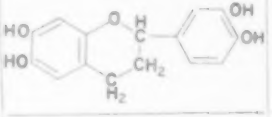
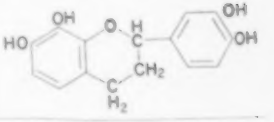
[1] T. A. Geissman und E. Hinreiner, *Bot. Rev.* **18,** 77 (1952). [2] Synthese: K. Weinges, *Liebigs Ann.*, **627,** 229 (1959); Naturstoff: A. K. Ganguly and T. R. Seshadri, *J. Sci. Industr. Res. India* B **17,** 168 (1958). [3] Naturstoff: M. Hasegawa, *J. Org. Chem.* **24,** 408 (1959).

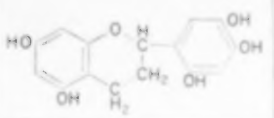
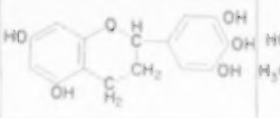
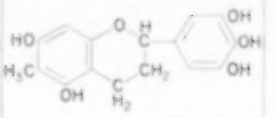
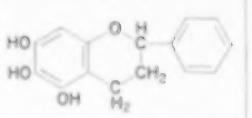
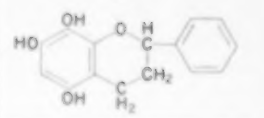
	2:1 	2:1 	2:2 
1	6,8-Dimethyl-5,7,4′-trihydroxy-flavan (25) 6,8-Dimethyl-pelargidan	7,8,4′-Trihydroxy-flavan (28)	5,7,2′,4′-Tetrahydroxy-flavan (1) 2′-Hydroxy-pelargidan
2			
3		(29) 7,8,4′-Trihydroxy-flavandiol (Teracacidin)[1]	(2) 2′-Hydroxy-pelargidandiol (3) 2′-Hydroxy-pelargidandiol-3,2′-äther ? 1766 (Cyanomaclurin)[2]
4	(26) 6,8-Dimethylpelargidanon 1616 (Farrerol) (27) 6,8-Dimethyl-pelargidanon-4′-methyläther 1617 (Matteucinol)		(4) 2′-Hydroxy-pelargidanon 1485 (Lotoflavin) (5) 2′-Hydroxy-pelargidanon-7-methyläther (Artocarpetin) Venk.
5			
6			
7			
8			(6) 2′-Hydroxy-pelargidanolon[3] (Dihydromorin)
9			(7) 2′-Hydroxy-pelargidenolon 1572 (Morin)

[1] J. W. Clark-Lewis, Privatmitteilung. [2] Wahrscheinlich 2′,3-Halb Ketal des 2′-Hydroxy-pelargidan-on-3. [3] W. R. Carruthers, R. H. Farmer and R. A. Laidlaw, *J. Chem. Soc.* 4440 (1957).

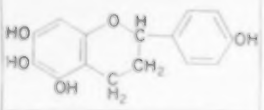
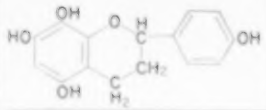
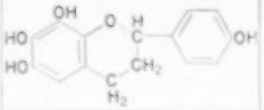
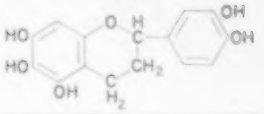
	
1	5,7,3′,4′-Tetrahydroxy-flavan (8) Cyanidan
2	(9) Cyanidanol 1762 (Catechin, Epicatechin) (10) Cyanidanol-3-methyläther 1765 (Aglykon des Arachidosids)
3	(11) Cyanidandiol 1757[1,2] (Leuko-cyanidin-hydrat, Leuko-cyanidin)
4	(12) Cyanidanon 1623 (Eriodictyol) (13) Cyanidanon-3-methyläther 1625 (Homoeriodictyol) (14) Cyanidanon-4′-methyläther 1626 (Hesperetin) (15) Cyanidanon-7,3′-dimethyläther[3] (16) Cyanidanon-7,3′-dimethyl-4′-isopentenyläther[3]
5	(17) Cyanidylin (Luteolinidin)
6	(18) Cyanidin 1712 (19) Cyanidin-3′-methyläther 1723 (Päonidin) (20) Cyanidin-7,3′-dimethyläther (Rosinidin)[4]
7	(21) Cyanidenon 1470 (Luteolin) (22) Cyanidenon-3′-methyläther 1481 (Chrysoeriol) (23) Cyanidenon-4′-methyläther 1479 (Diosmetin)[5]
8	(24) Cyanidanolon 1637 (Taxifolin) (25) Cyanidanolon-3-methyläther, Sesh. 198 (Dihydro-quercetin-3-methyläther) (26) Cyanidanolon-7-methyläther, Sesh. 198 (Dihydro-rhamnetin)
9	(27) Cyanidenolon 1522 (Quercetin) (28) Cyanidenolon-5-methyläther 1536a (Azaleatin) (29) Cyanidenolon-7-methyläther 1537 (Rhamnetin) (30) Cyanidenolon-3′-methyläther 1539, 1542 (Isorhamnetin) (31) Cyanidenolon-4′-methyläther 1548 (Tamarixetin) Venk. (32) Cyanidenolon-7,3′-dimethyläther 1546, 1543, 1547 (Rhamnazin) (33) Cyanidenolon-7,4′-dimethyläther 1550 (Ombuin) (34) Cyanidenolon-3,7,4′-trimethyläther 1552 (Ayanin)

[1] Synthese: K. Freudenberg u. K. Weinges, *Liebigs Ann.* **613,** 61 (1958). [2] Naturstoff: A. K. Ganguly u. T. R. Seshadri, *Tetrahedron* **6,** 21 (1959). [3] T. A. Geissman, *Aust. J. Chem.* **11,** 376 (1958). [4] J. B. Harbone u. H. S. A. Sherratt, *Nature, Lond,* **181,** 25 (1958) [5] J. H. Looker u. M. J. Holm, *J. Org. Chem.* **24,** 1019 (1959)

	2:2 	2:2 	2:2 	2:2 	2:2 
1	6-Methyl-5,7,3′,4′-tetrahydroxy-flavan. (35) 6-Methylcyanidan	6,8-Dimethyl-5,7,3′-4′-tetrahydroxy-flavan. (37) 6,8-Dimethylcyanidan	(39) 5,8,3′,4′-Tetrahydroxy-flavan	6,7,3′,4′-Tetrahydroxy-flavan. (41) 6-Hydroxy-fisidan	7,8,3′,4′-Tetrahydroxy-flavan. (43) 8-Hydroxy-fisidan
2					
3					(44) 8-Hydroxy-fisidan-diol 1759 (Melacacidin)
4		(38) 6,8-Dimethylcyanidanon, Sesh, 198 (Cyrtominetin)		(42) 6-Hydroxy-fisidanon 1630 (Platymenin)	(45) 8-Hydroxy-fisidanon-8-methyläther 1631(Methoxy-butin) (46) 8-Hydroxy-fisidanon-tetramethyläther 1632.
5					
6					
7					
8					
9	(36) 6-Methyl-cyanidenolon 1583 (6-Methyl-quercetin, Pino-quercetin)		(40) 5,8,3′,4′-Tetrahydroxy-flavenolon 1553 (5,8,3′,4′-Tetrahydroxy-flavonol)		(47) 8-Hydroxy-fisidenolon 1553a (7,8,3′,4′-Tetrahydroxy-flavonol, (Melanoxetin) Venk.

	2:3 	2:3 	2:3 	3:0 	3:0 
1	5,7,3′,4′,6′-Pentahydroxy-flavan (1) 6′-Hydroxy-cyanidan	5,7,3′,4′,5′-Pentahydroxy-flavan. (3) Delphidan	6-Methyl-5,7,3′,4′,5′-Pentahydroxy-flavan. (14) 6-Methyldelphidan	5,6,7-Trihydroxy-flavan. (1) 6-Hydroxy-chrysidan	5,7,8-Trihydroxy-flavan. (4) 8-Hydroxy-chrysidan
2		(4) Delphidanol 1767 (Gallocatechin)			
3		(5) Delphidandiol 1758[1] (Leuko-delphinidin, Leuko-delphinidin-hydrat)			
4					(5) 8-Hydroxy-chrysidanon-8-methyläther, Sesh. 198 (Dihydro-wogonin)
5					
6		(6) Delphidin 1727 (Delphinidin) (7) Delphidin-3′-methyläther 1742 (Petunidin) (8) Delphidin-3′,5′-dimethyläther 1746 (Malvidin) (9) Delphidin-7,3′,4′-trimethyläther 1752 (Hirsutidin)			
7		(10) Delphidenon (11) Delphidenon-3′,5′-dimethyläther 1488 (Tricin)		(2) 6-Hydroxy-chrysidenon 1442 (Baicalein) (3) 6-Hydroxy-chrysidenon-6-methyläther 1445 (Oroxylin A)	(6) 8-Hydroxychrysidenon Wogenon-8-methyläther 1446 (Wogonin)
8		(12) Delphidanolon 1640 (Ampelopsin)			
9	(2) 6′-Hydroxy-cyanidenolon-3,7,4′-trimethyläther 1579 (Oxyayanin A)	(13) Delphidenolon 1573 (Myricetin)	(15) 6-Methyldelphidenolon 1584 (Pinomyricetin)		

[1] Naturstoff: A. K. Ganguly, T. R. Seshadri u. P. Subramanian, *Tetrahedron* **3**, 225 (1958); D. E. HATHWAY, *Biochem. J.* **70**, 34 (1958).

	3:1 	3:1 	3:1 	3:2 
1	5,6,7,4′-Tetrahydroxy-flavan. (1) 6-Hydroxy-pelargidan	5,7,8,4′-Tetrahydroxy-flavan. (6) 8-Hydroxy-pelargidan	(13) 6,7,8,4′-Tetrahydroxy-flavan	5,6,7,3′,4′-Penathydroxy-flavan. (1) 6-Hydroxy-cyanidan
2				
3				
4		(7) 8-Hydroxy-pelargidanon 1614 (Carthamidin)		
5				
6				
7	(2) 6-Hydroxy-pelargidenon 1465 (Scutellarein) (3) 6-Hydroxy-pelargidenon-6,4′-dimethyläther 1467 (Pectolinarigenin)			
8		(8) 8-Hydroxy-pelargidanolon-8,4′-dimethyläther Sesh. 198 (Dihydro-herbacetin-8,4′-dimethyläther)		
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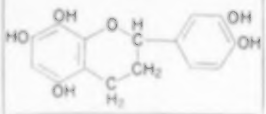
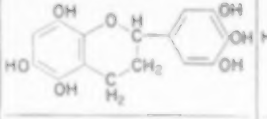
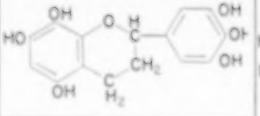
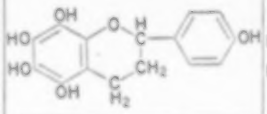
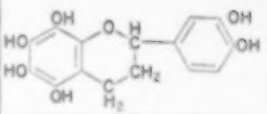
	3:2 	3:3 	3:3 	4:1 	4:2 
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[1] (12a) 8-Hydroxy-cyanidenolon-8,3′-dimethyläther (Limocitrin); R. M. Horowitz, *J. Amer. Chem. Soc.* **79**, 6561 (1957).

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FURTHER CONSIDERATIONS ON OXIDATIVE PROCESSES

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(*Received* 5 *September* 1959)

Abstract—Refuting recent criticisms by Russell, modification of the currently accepted mechanism of formation of benzyl chloride from toluene is introduced and current interpretation of the reactivity of carbonyl compounds is broadened. The results of the photochemical interaction of benzophenone, isopropyl alcohol, and nitric oxide are shown to accord with classical as against the hydrogen-abstraction theory of oxidation. Supplementary discussion of the behaviour of ethers, amines and paraffins is also contributed.

THE author's recent criticism[1] of the hydrogen-abstraction theory of oxidation has evoked renewed advocacy by Russell[2] of a version originally formulated by Russell and Brown[3] to cover the results of studies of competitive photohalogenation of toluene and cyclohexane at 80°.

In the first place, then, it must be emphasized that any such version is philosophically objectionable since it clearly assumes an essential difference between the courses of oxidation of inorganic and organic substances. Secondly, and consistently with this, the considerations by which Russell seeks to sustain his views are fallacious.

The admittedly generally accepted view that the side-chain photohalogenation of toluene proceeds directly and, apart from inductive effects, independently of the nucleus, is doubtful. It ignores the warning, to be derived from Faraday's ancient observation of the photochemical formation of hexachlorides from benzene,[4] that a similar reaction may occur with toluene. The cogency of this is supported by photo displacement from bromobenzene[5] and *p*-bromotoluene[6] of bromine by chlorine. The formation of *p*-chlorobenzyl bromide in the second case indicates displacement of atomic bromine. Similar results follow the chlorination of boiling *p*-bromotoluene[7] so that the observation by Asinger[8] of displacement of bromine from 3-chloro-5-bromo-toluene[9] at 180–190° is significant as evidence that the reaction depends, not on a simple replacement resulting from directive substitution, but on decomposition of an additive product. In fact α-benzene hexachloride melts with decomposition;[10] further, Barton *et al.* showed such decomposition of 1,2-dichloro-, 1,1,2-trichloro-, and 1,1,2,2-tetrachloro-ethanes to involve formation of atomic chlorine.[11] Similarly the writer, apropos of the thermal decomposition of tolane tetrachloride,[12] noted the

[1] J. Kenner, *Tetrahedron* **3**, 78 (1958).
[2] G. A. Russell, *Tetrahedron* **5**, 101 (1959).
[3] G. A. Russell and H. C. Brown, *J. Amer. Chem. Soc.* **77**, 4578, (1955).
[4] M. Faraday, *Ann. Chim. Phys.* (2) **30**, 274 (1825); H. P. Smith, A. A. Noyes and E. T. Hart, *J. Amer. Chem. Soc.* **55**, 4444 (1933).
[5] A. Eibner, *Ber. Dtsch. Chem. Ges.* **36**, 1230 (1903).
[6] O. Sprek, *Monats.* **11**, 431 (1890).
[7] G. Errera, *Gazz.* **17**, 202 (1887).
[8] F. Asinger, *Monats.* **64**, 153 (1934).
[9] cf. C. Walling and E. A. McElhill, *J. Amer. Chem. Soc.* **73**, 2927 (1951); B. Miller and C. Walling, *Ibid.* **79**, 4187 (1957).
[10] F. E. Matthews, *J. Chem. Soc.* **59**, 166 (1891); J. Meunier, *Ann. Chim. Phys.* (6) **10**, 234 (1887).
[11] D. R. Barton *et. al.*, *J. Chem. Soc.* 148, 155, 165, (1949).
[12] J. Kenner and E. Witham, *J. Chem. Soc.* 1960 (1910).

presence of chlorine and formation of benzoyl chloride,[13] during the thermal decomposition of αα-dichlorobenzylphenyl ketone. There is thus every reason to suppose, subject to more detailed study, some occurrence of such reactions during photohalogenation of toluene at 80°. In this case, and since the same cannot apply to cyclohexane, the above mentioned formulation of Russell and Brown is based on the treatment as comparable of reactions essentially different.

This also applies to Russell's comparative treatment of the photochalogenation of carboxylic acids and their reaction with acetylperoxide. This latter involves α-attack, followed by dimerization, and was attributed by Kharasch and Gladstone[14] and by Price and Moritz[15] to attack by methyl radicals derived from the peroxide. The reaction is, however, limited to the α-position and accordingly Occam's razor demands its consideration in this context. Now, in all cases of α-attack by a single molecule, whether of $\rangle CH-\overset{|}{C}-O$ or of $\rangle CH-\overset{|}{C}=C\langle$, one portion of it causes (1) electron disturbance of the carbonyl group or double bond, (2) removal of proton. The other portion then remains as an atom or radical which, if suitable, completes the process of α-substitution. Thus we have

$$-CH_2-CH=CH- + BrN\langle^{CO\cdot CH_2}_{CO\cdot CH_2} \rightarrow -CH_2-\dot{C}H-\dot{C}H + \bar{N}\langle^{CO\cdot CH_2}_{CO\cdot CH_2} + \cdot Br$$

$$\cdot Br + -CH=CH-\dot{C}H + HN\langle^{CO\cdot CH_2}_{CO\cdot CH_2}$$

The α-benzoxylation of olefins by benzoyl peroxide is accompanied by polymerization of the intermediate unsaturated radical.[16] Similarly the process of α-substitution is not completed when acetyl peroxide acts on carboxylic acids:—

$$\rangle CH\cdot C(OH)=O + (CH_3COO)_2 \rightarrow \rangle CH\cdot\dot{C}(OH)O\cdot + CH_3\bar{C}OO + CH_3COO\cdot$$

$$\rangle C\cdot C(OH)=O \leftarrow \rangle C=C(OH)O\cdot + CH_3CO_2H + CH_3COO\cdot$$

Dimer

It will be noted that molecular bromine does not meet the above conditions and its interaction with carbonyl compounds may be represented as follows:—

$$\rangle CH\cdot CO + Br_2 \rightleftarrows \rangle C=COBr + HBr$$

Thus α-substitution by bromine requires the auxiliary presence of acid or base.

In default, then, of satisfaction of the conditions necessary for α-substitution. e.g. by atomic chlorine, electrophilic attack must proceed by direct substitution, This probably also accounts for the methyl ketones obtained by Dakin from the action of hydrogen peroxide on ammonium carboxylates[18]:—

$$X\cdot CH_2CH_2\cdot C\bar{O}O + 2\cdot OH \rightarrow X\cdot CHOH\cdot CH_2\cdot C\bar{O}O$$

$$X\cdot CO\cdot CH_3 \leftarrow X\cdot CO\cdot\dot{C}H_2C\bar{O}O$$

[13] J. Kenner, unpublished observation.
[14] M. S. Kharasch and M. J. Gladstone, *J. Amer. Chem. Soc.* **65**, 15 (1942).
[15] C. C. Price and H. Moritz, *J. Amer. Chem. Soc.* **75**, 3686 (1952).
[16] cf. J. Kenner, *loc. cit.*
[17] A. Michael, *Ber. Dtsch. Chem. Ges.* **34**, 4028 (1901); M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.* **62**, 925 (1950).
[18] H. D. Dakin, *J. Biol. Chem.* **4**, 77, 91, 419 (1908); *Amer. Chem. J.* **44**, 41 (1910).

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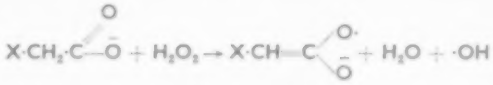
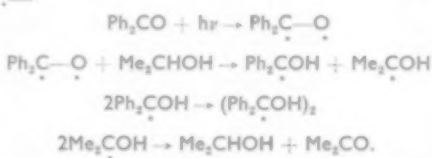
α-Attack also occurs and may supply the hydroxyl radicals requisite for the β-oxidation:



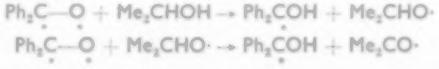
Similarly it appears that the attack of alcohols by hydroxyl is not limited to the hydroxy group or adjoining carbon atom.[19] The work of Westheimer[20] has illustrated the dual character required of reagents for the oxidation of alcohols.

The evidence adduced by Bridge and Porter,[21] of hydrogen-abstraction in the oxidation of alcohols by excited quinones also requires consideration. The reaction is not, as might be inferred from the title of their paper, limited to quinones and dyes, for Ciamician and Silber[22] recorded its occurrence with excited ketones and with benzaldehyde. Moreover the relative simplicity of the monocarbonyl compounds renders them more suitable than quinones for study of the essential mechanisms involved. Accordingly the oxidation of isopropyl alcohol by benzophenone, as recorded by Ciamician and Silber, was studied more closely by Bäckström[23] and formulated as follows:—



The products are tetraphenyl-glycol and acetone and Bäckström was thus constrained to postulate dismutation of $Me_2\dot{C}OH$. Although such a change has been recorded in the case of sodium diphenyl ketyl:[24]

it only occurs under alkaline conditions.[25] The formation of tetraphenyl-glycol in Bäckström's experiment shows the absence of conditions for dismutation and his formulation thus to be unacceptable. By contrast, the classical mechanism, involving contemporaneous electron and proton transference meets the experimental facts quite satisfactorily:



More recently, Bäckström *et al.*[26] have performed the same reaction in presence of nitric oxide, observing extensive formation of isopropyl nitrite, as would be anticipated if isopropoxy radical were an intermediate product. They were, however, unwilling to accept this interpretation because the products also included equimolecular quantities of nitrogen and nitrous oxide. Further, however, benzophenone was recovered unchanged and acetone was also produced. At least a qualitative

[19] cf. *Nature, Lond.* **182,** 366 (1958).
[20] F. H. Westheimer, *Chem. Rev.* **45,** 419 (1949); F. Holloway, M. Cohen and F. H. Westheimer, *J. Amer. Chem. Soc.* **73,** 65, (1951).
[21] N. K. Bridge and G. Porter, *Proc. Roy. Soc.* A **244,** 259, (1958).
[22] G. Ciamician and P. Silber, *Ber. Dtsch. Chem. Ges.* **34** 1530 (1901).
[23] H. L. J. Bäckström, *Svedberg Memorial Vol.* 456, (1944).
[24] E. Beckmann and T. Paul, *Liebigs Ann.* **266,** 1 (1891); W. Schlenk and P. Weickel, *Ber. Dtsch. Chem. Ges.* **44,** 1182 (1911); M. Gomberg and W. E. Bachmann, *J. Amer. Chem. Soc.* **49,** 236 (1926).
[25] W. E. Bachmann, *J. Amer. Chem. Soc.* **55,** 1179 (1932).
[26] H. L. J. Bäckström, A. Steneyr and P. Perlman, *Acta Chim. Scand.* **12,** 8 (1951).

explanation of these results is readily available as follows:

$$Ph_2\dot{C}OH + NO \rightarrow Ph_2C\begin{matrix}OH\\NO\end{matrix} \rightarrow Ph_2CO + HNO$$

$$Me_2CHONO \rightarrow Me_2CO + HNO$$

Thompson and Dainton[27] found the photochemical decomposition of alkyl nitrites to proceed according to the second of these equations and to yield much nitrogen and nitrous oxide derived, as they suggest, from decomposition of HNO.

It can thus hardly be doubted that the above reactions simply depend on photostimulation of the normal electrophilic property of benzophenone and that a similar conclusion applies to the photochemical behaviour of ketones and quinones generally. Here it is significant that stimulation by appropriate substitution has a similar effect. Thus Braude *et al.*[28] found tetrachloro-*o*-quinone to oxidise unsaturated alcohols in the dark.

It thus appears that Bridge and Porter's experiments merely amount to illustration of the fact that extrusion of proton is contemporaneous with removal of an electron from the oxygen atom of an alcohol. Their repeated references to hydroxylation of quinones by alkali are also presumptive evidence of the attack of hydroxy-compounds by quinones through oxygen.*

The above conclusion in regard to the chemical behaviour of excited carbonyl compounds and quinones gives added significance to the other observations of Ciamician and Silber. Thus their observation that the reaction of moist ether with excited carbonyl compounds yields the same products as alcohol is readily explained:

$$\dot{C}{-}\dot{O} + OEt_2 \rightarrow \dot{C}{-}\bar{O} + \dot{O}Et_2$$

$$\dot{C}{-}\bar{O} + H_2O \rightarrow \dot{C}OH + H_2C{=}CH_2 + \cdot OEt$$

$$\dot{C}{-}\bar{O} + H_2O \rightarrow \dot{C}{-}OH + EtOH$$

From anhydrous ether condensation products, presumably of acetaldehyde and ethylene were obtained.

The cleavage of ethers by radicals either directly by use of t-butyl peroxide[29] or indirectly by a mixture of alkyl halide with the corresponding Grignard compound in presence of cobaltous chloride,[30]† falls into the same category.

* It must further be added that their experiments, though initiated to elucidate the mechanism of oxidative tendering of cellulose by anthraquinone dyestuffs, were mainly carried out with duroquinone. At the outset Cooper (private communication) reported this quinone not to exhibit the oxidative behaviour of the tendering quinones towards alcohol.

† The interpretation of the genesis of radicals in this manner [R. O. C. Norman and W. A. Waters, *J. Chem. Soc.* 1950 (1957)] requires revision as follows in the light of the formation of diphenyl from phenyl magnesium bromide by treatment with chromic [G. M. Bennett and E. E. Turner, *J. Chem. Soc.* 1057 (1914)] or cupric chloride [J. Krizewsky and E. E. Turner, *Ibid.* 559 (1919)]:—

$$R\,Cl + CoCl_2 \rightarrow R\cdot + CoCl_3$$

$$RMgBr + CoCl_2 \rightarrow R\cdot + MgBrCl + CoCl_2$$

M. S. Kharasch and R. L. Huang, *J. Org. Chem.* **17**, 669 (1952)) have claimed the cleavage of ethers by the Grignard reagent and cobaltous chloride but a considerable excess of these reagents was used and M. S. Kharasch and Reinmuth, *Grignard Reactions of Non-metallic Substances.* Prentice-Hall, New York (1954) recognized the presence of perhaps 20 per cent of the original unused halide in Grignard reagents.

[27] H. W. Thompson and F. S. Dainton, *Trans. Faraday Soc.* **33**, 1546 (1937); cf. P. Gray and M. W. T. Pratt, *6th Symposium on Combustion* p. 183. Reinhold (1956).

[28] E. A. Braude, H. P. Linstead and K. R. H. Wooldridge, *J. Chem. Soc.* 3070 (1956).

[29] R. L. Huang and S. S. Si-Hoe, *Proc. Chem. Soc.* 354 (1951).

[30] M. S. Kharasch and R. L. Huang, *J. Org. Chem.* **17**, 669 (1952); R. L. Huang, *J. Chem. Soc.* 3084 (1954); R. L. Huang and S. S. Si-Hoe, *Ibid.* 3988 (1957).

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The possibility that the thermal decomposition of ether also may be initiated at the oxygen atom[31] has been recognized by Freeman.[32] In fact this and the reactions just discussed correspond to the ionization of the sodium atom alternatively by heat or by electrophilic agents.

Here it must be pointed out that in direct contrast to the foregoing treatment of the reactivity of ethers, it has been suggested that they act as electron acceptors in reductive cleavage by a solution of sodium in ammonia.[33] This view, however, is not only suspect in the light of Occam's razor but also, in its application to the case of 4-methoxy-diphenyl ether,

is at variance with the reducing power of hydroquinone monomethyl ether towards ammoniacal silver nitrate.[34] It would therefore seem that such metal-ammonia reductions must be attributed to atomic hydrogen, either actual or perhaps, in view of the colour changes noted in the reduction of naphthalene,[35] potential. The reduction of aromatic nuclei, acting as electron donors in covalent binding of hydrogen, should, as observed by Wooster,[36] be promoted by presence of an alcohol, acting as electron donor and source of proton:

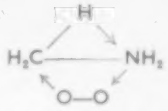
The complete elucidation of the reduction process must, however, await that of the nature of metal-ammonia solutions and of the related mechanism of the action of H_3O^+ on metals.

The comparison of amines with alcohols and ethers in respect of oxidation[37] is further illustrated by the behaviour of triethylamine towards chloranil.[38] On the other hand, but without regard for organic-chemical data, Cullis *et al.*[39] have interpreted the thermal reaction of amines with oxygen in terms of hydrogen-abstraction. Yet the formulation of ammonia in 90 per cent yield in the early stage of reaction with methylamine at 350° surely points to a simple reaction involving transfer of hydrogen from carbon to nitrogen:

$$H_2C{\cdot}NH_2 + O_2 \rightarrow H_2\overset{\cdot}{C}{\cdot}NH_2 + \bar{O}_2 \rightarrow H_2C{\cdot}\overset{\cdot}{N}H_2 + O_2$$
$$H_2CO + O \leftarrow H_2CO_2 + NH_2$$

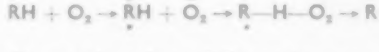
[31] J. Kenner, *loc. cit.*
[32] G. R. Freeman, *Proc. Roy. Soc.* **245**, 60 (1958).
[33] cf. A. J. Birch, *Quart. Rev.* **4**, 73 (1950).
[34] H. H. C. Hlasiwetz and J. Habermann, *Liebigs Ann.* **246**, 340 (1875).
[35] N. D. Scott, J. F. Walker and V. L. Hansley, *J. Amer. Chem. Soc.* **58**, 2442 (1935); W. Hückel and H. Bretschneider, *Liebigs Ann.* **540**, 157 (1939).
[36] C. B. Wooster, U.S. Pat. 2182242 (1938); A. J. Birch, *J. Chem. Soc.* 430 (1944).
[37] J. Kenner, *loc. cit.*
[38] D. Buckley, S. Dunstan and H. D. Henbest, *J. Chem. Soc.* 4880 (1957).
[39] C. F. Cullis and J. P. Willsher, *Proc. Roy. Soc.* A **209**, 218 (1951); C. F. Cullis and B. J. Waddington, *Ibid.* **244**, 110 (1958); **246**, 91 (1958); **248**, 316 (1958).

The occurrence of this series of electronic transferences in the gas phase is readily accommodated within the complex



This would also explain the transition from a slow induction period[40] by the genesis of atomic oxygen.

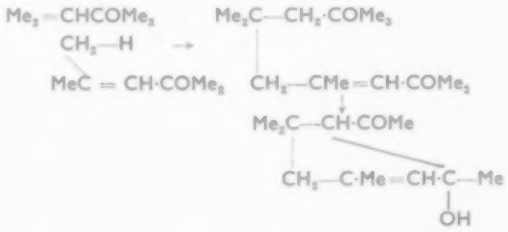
Ciamician and Silber also showed the oxidizing action of excited quinone to be effective in the cases of hexane and octane.[41] This evidence, together with that of charge-transfer between oxygen and paraffins[42] is in contrast with current neglect of the significance in this matter of electron-transference,[43] and accords with the scheme already advanced.[44]



Insistence on the diagnostic value of Occam's razor has pervaded the foregoing discussion and the earlier paper. Two instances of its more general application are therefore appended:—

(1). The apparently anomalous *meta*-chlorination of chloro-and bromo-benzenes above 450° [45] are probably attributable to isomerization of the normal *para*-product by hydrogen chloride. Baddeley and Kenner[46] demonstrated the conversion of *p*-di-n-propyl benzene into its *meta*-isomeride by aluminium chloride.

(2). Braude *et al.* regarded the dimerization of mesityl oxide in presence of lithium as "a novel type of diene addition.[47]" The first stage of the reaction is, however, evidently an expanded or vinylogous form of the Michael reaction, just as the latter is an expanded form of the aldol reaction:—



The second stage is a normal aldol reaction.

[40] L. J. Jolley, *J. Chem. Soc.* 1957 (1934).
[41] G. Ciamician and P. Silber, *loc. cit.*; cf. N. K. Bridge and G. Porter, *loc. cit.*
[42] A. D. Munck and J. F. Scott, *Nature, Lond.* **177**, 587 (1956); cf. D. F. Evans, *J. Chem. Soc.* 4229 (1957).
[43] e.g., C. F. H. Tipper, *Quart. Rev.* **11**, 313 (1957).
[44] J. Kenner, *loc. cit.*; cf. A. D. Walsh, *Trans. Faraday. Soc.* **42**, 269, (1946).
[45] J. P. Wibaut, L. M. F. Lande and G. Wallagh, *Rec. Trav. Chim.* **51**, 381, 940 (1933); J. P. Wilbaut and M. van Loon, *Ibid.* **56**, 815 (1937).
[46] G. Baddeley and J. Kenner, *J. Chem. Soc.* 633 (1934).
[47] E. A. Braude, B. F. Gofton, G. Lowe, and E. S. Waight, *J. Chem. Soc.* 4054 (1956).

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CHEMISTRY OF THE PODOCARPACEAE—V*

THE IDENTIFICATION OF MIROPINIC ACID AND ISOMIROPINIC ACID FROM *PODOCARPUS FERRUGINEUS* D. DON

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(*Received* 10 *September* 1959)

Abstract—By reinvestigation of "isomiropinic" and "miropinic" acids from the bled resin of *Podocarpus ferrugineus*, the compounds have been identified as sugiol and isopimaric acid respectively. The identity of the resin acid from *Dacrydium biforme* has been confirmed as isopimaric acid.

DURING a separation of the constituents from the bled resin of the New Zealand species *Podocarpus ferrugineus* D. Don (Maori name "Miro"), Brandt and Neubauer isolated, along with the diterpenoid resinol, ferruginol,† a resin acid fraction in smaller yield.[1] Subsequent investigation[2] showed it to be comprised of two crystalline compounds, "miropinic acid", the major constituent, and "isomiropinic acid", obtained in much lower yield. "Miropinic acid", $C_{20}H_{30}O_2$, m.p. 160°, $[\alpha]_D^{16}$ −3·6°, yielded, on catalytic hydrogenation in neutral solvent, two isomeric dihydro-acids each of which in turn gave rise to different saturated tetrahydro-acids together with a small amount of a third dihydro-isomer, on further hydrogenation in acetic acid solution. "Miropinic acid" formed a liquid methyl ester and when dehydrogenated with selenium it yielded pimanthrene. Further, the melting point of "miropinic acid" was undepressed by an unnamed acid isolated by Hosking and Brandt from the related species *Dacrydium biforme* Pilger[3] and also by Hosking from *Dacrydium kirkii* F. Muell.[4] From these results they concluded that "miropinic acid" was either identical or stereoisomeric with the acids from *D. biforme* and *D. kirkii* and might be identical with cryptopimaric acid, m.p. 159–161°, $[\alpha]_D^{16\cdot3}$ −20·83°, $[\alpha]_D^{17\cdot5}$ −18·99°, from *Cryptomeria japonica*.[5] Jeger and Brossi[6] subsequently reported that "miropinic acid" was identical with isopimaric (isodextropimaric) acid‡ by direct comparison of the acids and their methyl esters and by comparison of the infra-red spectra of the methyl esters.

* Part IV. L. H. Briggs, R. C. Cambie, R. N. Seelye and A. D. Warth, *Tetrahedron* **7**, 270 (1959).

† Bredenberg (ref 12) has shown that this compound contains small amounts of Δ^9-dehydroferruginol.

‡ In accord with E. Wenkert and J. W. Chamberlin, *J. Amer. Chem. Soc.* **81**, 688 (1959); Le Van Thoi, *C.R. Acad. Sci., Paris* **247**, 1343 (1958) and O. E. Edwards and R. Howe, *Chem. & Ind.* 537 (1959) the simplified name is used throughout.

[1] C. W. Brandt and L. G. Neubauer, *J. Chem. Soc.* 1031 (1939).
[2] C. W. Brandt and L. G. Neubauer, *J. Chem. Soc.* 683 (1940).
[3] J. R. Hosking and C. W. Brandt, *Chem. Ber.* **68**, 1313 (1935).
[4] J. R. Hosking, *New Z. J. Sci. and Tech.* **19**, 208 (1937).
[5] S. Keimatsu, T. Ishiguro and G. Fukuri, *J. Pharm. Soc. Japan* **57**, 69 (1937).
[6] A. Brossi and O. Jeger, *Helv. Chim. Acta* **33**, 722 (1950).

"Isomiropinic acid", $C_{20}H_{30}O_2$, m.p. 284°, $[\alpha]_D^{17}$ +21·2°, was obtained directly from the resin acid mixture and was also reported as being produced by the isomerization of "miropinic acid" with methanolic hydrogen chloride.* On catalytic reduction it gave a neutral resin, $C_{20}H_{30}O$, which was not investigated further.

In our continued investigation of the extractives of the New Zealand *Podocarpaceae* it appeared desirable to confirm Brossi and Jeger's conclusion regarding the nature of "miropinic acid". It may be pointed out that Brossi and Jeger did not in reality compare isopimaric and "miropinic" acids. What they did compare with the former acid was the unnamed resin acid from *D. biforme* which they assumed to be identical with "miropinic acid" from *D. ferrugineus*. In view of the difficulties encountered in the separation of pure resin acids this assumption is not necessarily valid. As Brandt and Neubauer realized, without a determination of the optical acitvity of the acid from *D. biforme*, "miropinic acid" could be a stereoisomer of it, despite the fact that no depression in melting point was observed on admixture. Furthermore, the infra-red spectra of the methyl esters published by Brossi and Jeger,[6] although very similar, are not coincidental at all points and could possibly be those of stereoisomers. During our investigations of the diterpene hydrocarbons[7,8] we have found that the stereoisomeric compounds phyllocladene, mirene and kaurene possess infra-red spectra which show only small differences in the "finger print" region, of order comparable to those exhibited by the above methyl esters.[6] If in fact "miropinic acid" is identical with isopimaric acid it also appeared necessary to explain if possible, the isomeric dihydro- and tetrahydro- derivatives of "miropinic acid", the isomerization of "miropinic acid" to "isomiropinic acid" and to reinvestigate the nature of "isomiropinic acid" itself, and also its hydrogenated product. For example, from the method of isolation of "isomiropinic acid" viz. by precipitation from a sodium hydroxide solution with carbon dioxide and from the insolubility of the hydrogenated product in aqueous sodium hydroxide it appeared doubtful that it was in fact a resin acid.

Fortunately, small samples of the original "miropinic acid" and "isomiropinic acid" isolated by Brandt and Neubauer from *Podocarpus ferrugineus*[2] were available for further study. Three recrystallizations of "isomiropinic" acid from glacial acetic acid raised the melting point to 292–293° and analysis favoured the formula, $C_{20}H_{28}O_2$, rather than $C_{20}H_{30}O_2$, as proposed by Brandt and Neubauer. Furthermore, it formed a crystalline acetate, m.p. 164–165°, slowly reacted with 2,4-dinitrophenylhydrazine reagent and possessed an ultra-violet spectrum (maxima at 233 mμ and 285 mμ) markedly different from that of isopimaric or pimaric acid.[9] These properties are in excellent agreement with those of the phenolic ketone, sugiol, isolated from the heartwood of *Podocarpus dacrydioides* A. Rich. (Part IV) and by Brandt and Thomas from the related species, *Dacrydium cupressinum* Soland.[10] The identification was confirmed by direct comparison and by identical infra-red spectra.

"Miropinic acid" was purified via the butanolamine salt and regeneration of the free acid by Harris and Sanderson's method.[9] It then had m.p. 162–164°, zero rotation

* It is assumed that the melting point of 184° recorded for the compound isolated in this manner is a misprint for 284°.

[7] L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, *Tetrahedron Letters* No. 8, 8, 13 (1959).
[8] L. H. Briggs, B. F. Cain and R. C. Cambie, *Tetrahedron Letters* No. 8, 17 (1959).
[9] G. C. Harris and T. F. Sanderson, *J. Amer. Chem. Soc.* **70**, 2079 (1948).
[10] C. W. Brandt and B. R. Thomas, *New Z. J. Sci. Tech.* **33B**, 30 (1951); *J. Chem. Soc.* 2442 (1952).

and an infra-red spectrum identical with that of isopimaric acid.* The infra-red spectra of the respective methyl esters were also identical.

Isopimaric and pimaric acid co-occur in other plants[9] but, in this case, pimaric acid could not be detected in the mother liquors from the purification of isopimaric acid.

In contrast to the two dihydro derivatives obtained by Brandt and Neubauer, partial hydrogenation of the purified acid under the conditions of Edwards and Howe[11] led to a dihydro derivative which had physical constants in excellent agreement with their dihydroisopimaric acid.

With the identification of "isomiropinic acid" and "miropinic acid" established as sugiol and isopimaric acid respectively, it now became possible to clarify some of the points raised earlier. The neutral resin, $C_{20}H_{30}O$, obtained by Brandt and Neubauer on catalytic hydrogenation of sugiol was apparently ferruginol formed by reduction of the keto-group to 9-oxyferruginol, followed by dehydration to the dehydro derivative and catalytic hydrogenation of the double bond. Bredenberg[12] has shown that reduction of sugiol with aluminium isopropoxide leads to a high yield of the dehydro derivative as a result of the ready dehydration of the intermediate 9-oxyferruginol. The identity of the neutral product was confirmed by repetition of the catalytic reduction of sugiol and isolation of ferruginol as its crystalline acetate.

Despite the fact that it has been shown that the original sample of "miropinic acid" was impure and that in our hands only a single dihydro derivative was obtained from the purified compound, the recent work of Edwards and Howe on the stereochemistry of the isomeric pimaric acids,[11,13] allows for a possible explanation of Brandt and Neubauer's three isomeric dihydro- and two isomeric tetrahydro-derivatives. These workers have shown that rigorously purified dihydroisopimaric acid has m.p. 173–175°, $[\alpha]_D$ −7°, while tetrahydroisopimaric acid has m.p. 172–173°, $[\alpha]_D$ +24°. However, it was observed that hydrogenation is accompanied by double bond migration to the Δ^{13}-dihydro compound, but that it was not possible to form the pure isomer on the catalyst surface. The physical constants of "α-dihydromiropinic acid", m.p. 176°, $[\alpha]_D$ −10·5°, and "α-tetrahydromiropinic acid", m.p. 170°, $[\alpha]_D$ +15·2°, correspond reasonably well with those of dihydro- and tetrahydroisopimaric acids, respectively, and are probably almost pure compounds. The physical constants of "β-dihydromiropinic acid", m.p. 115°, $[\alpha]_D$ +23·2°, suggest that it may be a mixture of isopimaric and Δ^{13}-isopimaric acids (m.p. 106–107°, $[\alpha]_D$ +113°), probably corresponding to the 1 : 1 synthetic mixture m.p. 118–120°, $[\alpha]_D$ +58°, of Edwards and Howe, with dihydroisopimaric as impurity. "γ-dihydromiropinic acid" could be a similar mixture or a mixture of dihydroisopimaric acid and Δ^{13}-dihydropimaric acid (m.p. 107–108°, $[\alpha]_D$ +74°[11]) while "β-tetrahydromiropinic acid", m.p. 170°, $[\alpha]_D$ +30·5°, may well be mainly tetrahydroisopimaric acid containing a trace of Δ^{13}-dihydroisopimaric acid as impurity.

Finally, purification of the resin acid from *Dacrydium biforme*, m.p. 148–150°, via the butanolamine salt, gave a pure compound, m.p. 162–164°, $[\alpha] \pm 0$, the infra-red

* See also comparisons of the spectra of the pimaric acids [H. H. Bruun, *Paper and Timber, Finland* **38**, 557 (1956); **39**, 221 (1957); H. H. Brunn, I. Fischmeister and E. Stenhagen, *Acta Chem. Scand.* **13**, 379 (1959)].

[11] O. E. Edwards and R. Howe, *Canad. J. Chem.* **37**, 760 (1959).
[12] J. B. Bredenberg, *Acta Chem. Scand.* **11**, 932 (1957).
[13] O. E. Edwards and R. Howe, *Chem. & Ind.* 629 (1958).

spectrum of which was identical with that of isopimaric acid, thus confirming Brossi and Jeger's identification of this compound.

EXPERIMENTAL

Analyses were by Dr. A. D. Campbell, University of Otago, New Zealand. Infra-red spectra were measured as KBr discs with a Beckman IR2 instrument (NaCl prism) and ultra-violet spectra for EtOH solutions with a Beckman DU instrument.

Sugiol. Three recrystallizations of "isomiropinic acid", m.p. 284°, from glacial acetic acid (charcoal) gave sugiol as long colourless needles, m.p. and mixed m.p. 292–293°, $[\alpha]_D^{20}$ +22·6° (*c* 1·2 in dioxan), $[\alpha]_D^{20}$ +34·2° (*c* 1·5 in pyridine) (Found: C, 80·0; H, 9·2; Calc. for $C_{20}H_{28}O_2$: C, 80·0; H, 9·4%). λ_{max} 233 mμ (log ε 4·21) and 285 mμ (log ε4·14), (identical infra-red spectrum). The acetate, prepared by the use of acetic anhydride–pyridine (100°; 2 hr), formed needles, m.p. and mixed m.p. 164–165°, from aqueous methanol.

Ferruginol. Sugiol (500 mg) was catalytically hydrogenated by the method of Brandt and Neubauer for "isomiropinic acid"[2] for 2 hr at room temp. Filtration and removal of solvent from the filtrate, followed by distillation of the oil obtained, gave ferruginol (210 mg), b.p. 180–200°/0·5 mm as a pale yellow resin. Acetylation by the method of Brandt and Neubauer[1] gave ferruginyl acetate (200 mg) which crystallized from ethanol (charcoal) as colourless rods, m.p. and mixed m.p. 80–81°.

Isopimaric acid. Combined crude samples of "miropinic acid" (600 mg) in methyl acetate (20 cc) were treated with 2-amino-2-methylpropan-1-ol (250 mg) in the same solvent (5 cc) according to the method of Harris and Sanderson.[9] After three recrystallizations as flat rods from a large volume of methyl acetate, the salt had m.p. 194–196°, with preliminary sintering, $[\alpha]_D^{20}$ ±0° (*c* 2·5 in EtOH). The isopimaric acid liberated from the salt, after four recrystallizations from 50% aqueous ethanol had m.p. and mixed m.p. 162–164°, $[\alpha]_D^{20}$ ±0° (*c* 1·31 in EtOH) (Found: C, 79·7; H, 9·6. Calc. for $C_{20}H_{30}O_2$: C, 79·4; H, 10·0%). The infra-red and ultra-violet spectra were each identical with the respective spectra of an authentic sample of isopimaric acid with the same physical constants.* The methyl ester prepared by the use of diazomethane had m.p. and mixed m.p. 60–61° (identical infra-red spectrum).

Isopimaric acid from Dacrydium biforme. A sample of resin acid, m.p. 148–153°, from *D. biforme*, was purified by the above method. After two recrystallizations from 50% aqueous ethanol it had m.p, and mixed m.p. 162–164°, $[\alpha]_D^{20}$ ±0° (identical infra-red spectrum).

Dihydroisopimaric acid. A solution of isopimaric acid (300 mg) in ethanol (20 cc) was hydrogenated in the presence of pre-reduced palladium charcoal catalyst (10%; 250 mg) at room temp for 10 min. Purification by chromatography on silica gel by Edward and Howe's method gave dihydroisopimaric acid (230 mg) as rods, m.p. 172–174°, $[\alpha]_D^{20}$ −7·6° (*c* 1·23 in EtOH) (Found: C, 79·1; H, 10·6. Calc. for $C_{20}H_{32}O_2$: C, 78·9; H, 10·5%).

Acknowledgements—The authors are grateful to the Hercules Powder Co., Delaware, for generous gifts of oleoresin from *Pinus palustris* and *Pinus carribaea* and to Mr. I. R. C. McDonald, Dominion Laboratory, Wellington, New Zealand for a sample of the resin acid from *Dacrydium biforme*. Assistance is also gratefully acknowledged from the Research Grants Committee of the University of New Zealand, the Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science and The Chemical Society.

* The authors are grateful to Dr. B. F. Cain and Mr. R. Robertson for the isolation and purification of isopimaric acid from the oleo resin of *Pinus palustris* and *Pinus carribaea* by the methods of G. C. Harris and T. F. Sanderson, *J. Amer. Chem. Soc.* **70**, 338, 2079 (1948). Purity and homogeneity of the acid had been shown by crystallization of the butanolamine salt to constant rotation followed by ten recrystallizations of the free acid.

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STEROID NOMENCLATURE

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Abstract—Proposals for revision of nomenclature are as follows:

1. In a sapogenin or alkaloid in which the terminal carbon is linked to a hetero atom, this carbon atom, in accordance with the Fischer convention, acquires the number 27.

2. If, in a Fischer projection of an open side chain, methyl or hydroxyl at a given center lies to the left it is β-oriented; if it lies to the right it is α-oriented.

3. In a sapogenin or alkaloid the true stereochemistry at any center in the side chain is described as the configuration at this center in the alcohol or amine derived by opening the side chain and making a Fischer projection. If the orientation so defined as α is down (or rear) it is described as α-oriented. The symbol α_F is used to indicate that the configuration by Fischer projection is α but that the orientation is up (or front).

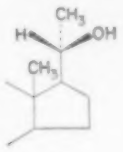
IN our book *Steroids*[1] we employed, without discussion, a system of nomenclature which departs in some respects from current usage, as set forth in the 1957 IUPAC Rules for Nomenclature of Steroids.[2] It is the purpose of this paper to discuss the various problems involved in the hope of stimulating general consideration of the matter and eventual agreement on one system or the other, or on a compromise. Actually the 1957 IUPAC Rules are essentially those formulated at a conference held in 1950 at the Ciba Foundation in London,[3] in which we participated. In view of the rapid advances in the steroid field over the past decade, this would seem an appropriate time to reconsider the proposals of 1950.

One rule recorded without comment and without any evident rationale is that in a sapogenin or related alkaloid the terminal carbon carrying the oxygen or nitrogen function be assigned the number 26. This assignment, however, violates the Fischer convention[4] that in determination of the basic carbon skeleton a terminal carbon carrying oxygen (or nitrogen) takes precedence over a methyl group. This convention was not defined as such by Fischer but merely implied by his usage, and although it is familiar to sugar chemists[5] it may not be generally known. Thus the convention was first called to our attention in very helpful discussions with T. Reichstein and with A. Georg. Since a convention does exist, we see no reason for not assigning the number 27 to the substituted terminal carbon.[6]

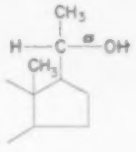
With steroids of the natural (or *d*-) series having an open side chain, assignment of configurations requires merely an extension of existing conventions. One,[7] applicable to pregnane-20-ols, calls for orienting the model with methyl (forming part of

[1] L. F. Fieser and M. Fieser, *Steroids*. Reinhold, New York (1959).
[2] International Union of Pure and Applied Chemistry, *Nomenclature of Organic Chemistry*, 1957. Butterworths, London (1958).
[3] See *Chem. & Ind.* SN 1, June 23 (1951); *Helv. Chim. Acta* **34**, 1680 (1951); *Bull. Soc. Chim. Fr.* No. 3/4 viii-ix (1951).
[4] E. Fischer, *Ber. Dtsch. Chem. Ges.* **24**, 1836, 2683 (1891).
[5] W. Pigman, *The Carbohydrates* p. 23. Academic Press, New York (1957).
[6] In application of the Fischer convention to sugars, the oxygenated carbon is assigned the number 1. With steroids, since it is impossible to use the lowest number, choice of the highest number (C_{27}) seems in keeping with the spirit of the convention.
[7] L. F. Fieser and M. Fieser, *Experientia* **4**, 285 (1948).

the longest chain) to the rear and hydrogen and hydroxyl to the front, as in I.



I



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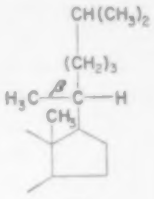
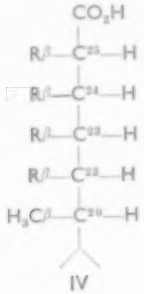
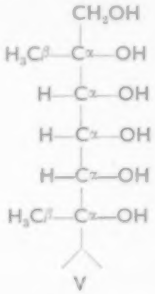


III

The Fischer projection is then made as in II, and the hydroxyl lying to the right is defined as α-oriented. A second convention, proposed by Pl. A. Plattner in an appendix to the Ciba conference report,[3] is that cholesterol, known to have the configuration III, be defined as having a 20β-methyl group. Obvious extensions for definition of the orientations of alkyl and hydroxyl groups at positions in the side chain are shown in IV and V. An alkyl group that is on the left, like the 20β-methyl



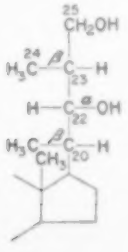
IV



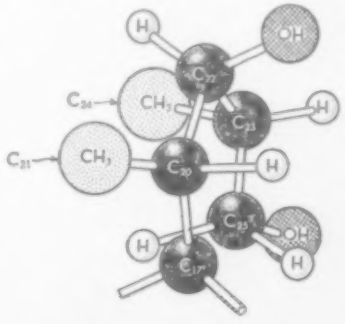
V

group, is described as β-oriented, one on the right is α-oriented. Hydroxyl groups lying to the right are α, to the left, β. Thus V has a 20β-methyl and a 20α-hydroxyl group. The diol derived from cholesterol by replacement of the 20α-hydrogen by hydroxyl without inversion is 20α-hydroxycholesterol; its 20-epimer is best described as 20β-hydroxy-20-isocholesterol.

In 20α-hydroxycholesterol the methyl at C_{20} is β-oriented and the hydroxyl is α-oriented, and it does not seem proper to describe carbon atom 20 as having either the α- or the β-configuration. The configuration is adequately defined by the orientation of groups, considered as substituents. In diol VI the configuration at C_{20} is indicated by description of the substance as of the 20β-methyl orientation, and the number (21)



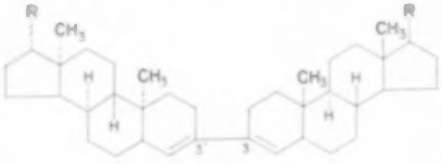
VI



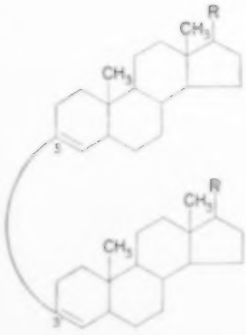
of the carbon of the methyl group need not appear in the name. The methyl group attached to C_{23} can similarly be regarded as a substituent, comparable to the substituent hydroxyl at C_{22}. Thus VI is a 20β, 24β-dimethyl-22α, 25-diol.

The proper way to view a model is shown in the drawing VII of the diol VI. The carbon atoms forming the basic chain are arranged in a plane so that the chain curves around to the rear. One views C_{20} from the front as usual, but to view other carbons one must float along the chain and look to the right and left as one passes over each station. When one reaches C_{23} one is upside down, but appropriately sees methyl to the left (β) and hydrogen to the right (α).

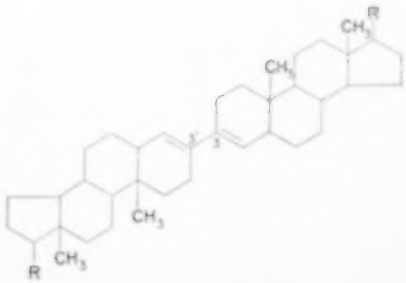
The α and β designations defined for an open side do not carry the implication of down (or rear) and up (or front) that is usually associated with similar designations at nuclear positions but they have the same status of defining the actual relative configurations. The configuration at a given center, once determined, is fixed and, in our view, is not altered by making rotations about single bonds, by turning a model upside down, or by the closing of rings in the side chain. This is the key point on which our view differs from that of the IUPAC. The problem is particularly pressing in the sapogenin and alkaloid series, but it may come up also with respect to positions in the ring system. In the bisteroid VIII the groups at positions 10, 8, 13, and 17 are β, and so, we think, are those at positions 10′, 18′, 13′, and 17′, even though they happen to be to the rear. J. Mathieu has pointed out in a letter that all the β-groups can be shown as oriented to the front by formulating the bisteroid as in IX, and Georg has noted that Chopin[8] and others achieve the same end with formula X. However VIII might be the formula of choice for certain discussions because it shows that the hydrocarbon has the potentiality for Diels–Alder reaction as a cisoid diene, and it



VIII



IX



X

[8] J. Chopin, *Bull. Soc. Chim. Fr.* 258 (1956).

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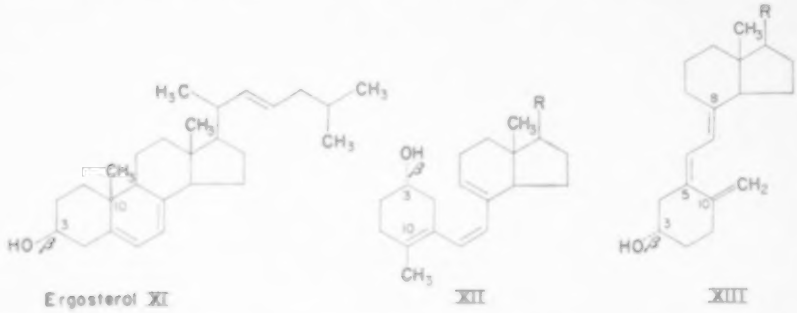
seems to us perfectly valid; one must simply recognize that in this case α and β denote configuration alone and not orientation in space.

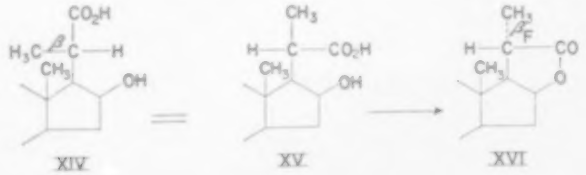
In the case of previtamin D_2 (XII) and vitamin D_2 (XIII) there is no alternative way of writing correct formulas that show the 3-hydroxyl group oriented to the front. One colleague, commenting on a first draft of this paper, suggested that *for nomenclature purposes* formulas (XII) and (XIII) be rotated about appropriate single bonds to give arrangements in which the carbon atoms are placed in the same way as in the conventional formulas of the steroids and in which the hydroxyl group is to the front. But vitamin D_2 would then be represented as having a cisoid diene system extending from C_8 to C_5 whereas X-ray and chemical evidence indicates that it is transoid. If it is indeed necessary to choose between correct chemistry and convenience of nomenclature, the former surely should prevail. To describe these isomers of ergosterol (XI) as having the 3α-configuration seems to us incorrect. The configuration at C_3 is



Ergosterol XI XII XIII

the same as in ergosterol, or β, and the compounds are adequately described as 3β-alcohols with a rear-oriented hydroxyl group. A β-label and a dotted bond show both the configuration and the orientation. Since bonds at ring positions ordinarily are not labeled, the appearance of the β on a bond which is dotted and hence to the rear shows at once that the case is a special one.

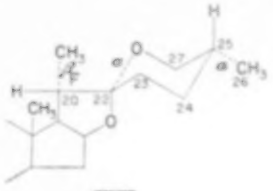
The same treatment seems to us a practical and accurate way of dealing with compounds having cyclized side chains, for example, the lactone XVI derived from the 16β-hydroxybisnor acid XIV, or its equivalent XV. The acid has a 20β-methyl group like cholesterol, and the configuration is retained on cyclization. To follow IUPAC and say that cyclization of a 20β-methyl hydroxy acid gives a 20α-methyl lactone does not seem rational. In this system a Greek letter indicates only that a group is up or down, (or front or rear) which can be seen in any case from the nature of the bond, and it has no reference to the actual configuration relative to other centers and other compounds. This abandonment of configurational indication seems to us a serious shortcoming of the system, and we see distinct advantages in an alternative system from which it is clear at a glance, for example, whether or not a given



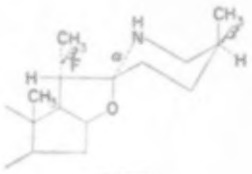
XIV XV XVI

alkaloid corresponds in configuration at a specific site to a sterol or a sapogenin. With a complicated molecule it may be necessary to build a model and open it up for projection in order to establish the configurations, but this operation need be performed only once. However, we are aware, particularly from comments by R. S. Cahn and by J. Fried, that many chemists have become too familiar with the simple "α-below and β-above the plane" nomenclature to be willing to give it up.

To resolve the impasse, we now suggest a compromise utilizing the symbols α_F and β_F suggested by J. Fried to indicate configurations as defined by the Fischer convention. We propose that, where the IUPAC and that the Fischer assignments are identical, the configuration (and orientation) be indicated by α or β, but that where a difference exists the designation be α_F or β_F. Thus cyclization of the 16β-hydroxybisnor acid XIV of 20β-configuration gives a lactone with an α-oriented $20\beta_F$-methyl group. Projection

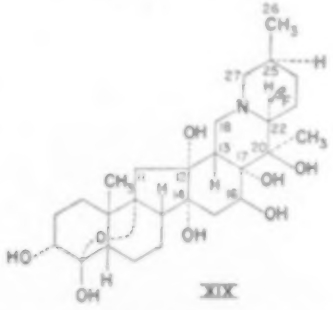


XVII



XVIII

of the opened-up forms of smilagenin (XVII) and of tomatidine (XVIII) shows that the bond extending from the hetero atom to C_{22} is α (rear) and that the 25-methyl group is α (down) in (XVII) and β (up) in (XVIII). Both the sapogenin and the alkaloid, however, have a rear-oriented $20\beta_F$-methyl group. In the case of cevine (XIX) and related alkaloids[9] the IUPAC system defines configurations identical with those derived by Fischer convention except at C_{22}; here the hydrogen is down but

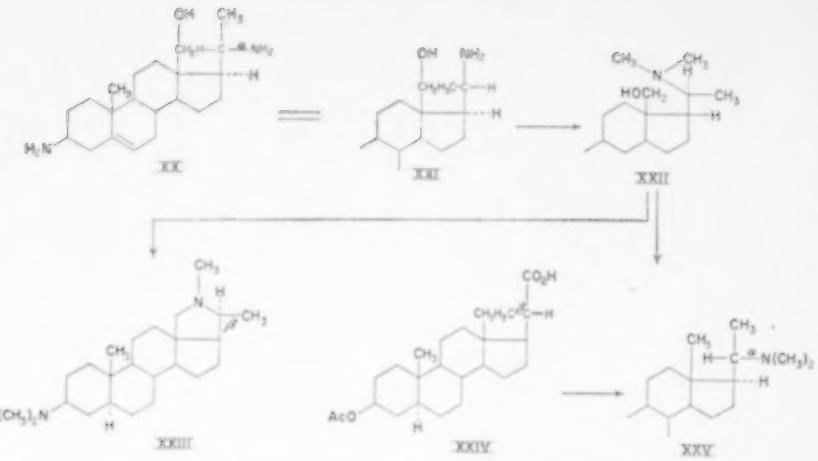


XIX

the configuration is $22\beta_F$-H. The alkaloid is unusual in that the configuration at C_{20} is the opposite of that of cholesterol and of other steroid alkaloids and of the sapogenins.

Holarrhimine (XX) has been correlated with conessine by cyclization of tetramethyldihydroholarrhimine (XXII) to a product identical with dihydroconessine (XXIII) and the configuration at C_{20} of both alkaloids was established by conversion of the 19-hydroxymethyl group of XXII to methyl (XXV) and synthesis of the latter compound from 3β-acetoxybisnorallocholanic acid (XXIV).[10] By the well established

[9] S. M. Kupchan, W. S. Johnson and S. Rajagopalan, *Tetrahedron* **7**, 47 (1959).
[10] V. Černý and F. Šorm, *Coll. Czech. Chem. Comm.* **20**, 1473 (1955); L. Labler, V. Černý and F. Šorm, *Ibid.* **20**, 1484 (1955); V. Černý, L. Labler and F. Šorm, *Ibid.* **22**, 76 (1957).



convention for 20-alcohols, holarrhimine (XX) is described as having a 20α-oriented amino group, the 20-hydrogen is β, and the 20-methyl group has no assignment. To meet the case at hand, we suggest that the formula be arranged as in (XXI) with the amino group at the top or rear, corresponding to the carboxyl group of the acid (XXIV) or C_{22} of the original cholesterol side chain. The 20-methyl group then corresponds to that of cholesterol, and in dihydroconessine (XXIII) retains the β-orientation in both the Fischer and the IUPAC sense.

In arriving at the present proposals, which supplement those of our book,[11] we have been guided, and in some cases corrected, by very helpful discussions with the commentators already mentioned as well as with R. E. Beyler, R. K. Callow, J. W. Cornforth, M. E. Wall, and O. Wintersteiner.

A further recommedation is with respect to chemical names in English. In the interest of preservation of some beauty in the language, we protest against current usage of such names as cholest-5-ene, cholest-5-en-3β-ol, pregna-5,16-dien-20-one, and urge adoption of the rule that a chemical name should be divided only when each part is a correctly pronounceable word in its own right. Cholest and pregna are not words. En and dien are not words and should be pronounced én and dién. On the other hand, ene diene, polyene are acceptable as properly pronounced words, as are ol, diol, triol. Suitable names for the compounds mentioned are: 5-cholestene or Δ⁵-cholestene, 5-cholestene-3β-ol, or Δ⁵-cholestene-3β-ol, 5,16-pregnadiene-20-one or Δ⁵,¹⁶-pregnadiene-20-one. We prefer use of the Δ, particularly since this prevents confusion of numbers; thus 3β-chloro-Δ⁵-cholestene seems better than 3β-chloro-5-cholestene. We are opposed also to the prevalent cholestan-3β-yl acetate. Cholestan is not a word and we see little to support the contention that yl is a word, certainly not a good word; diyl and triyl do not exist. Cholestanyl acetate is assuredly correct, but for a specific name we prefer cholestane-3β-ol acetate, to be read in the sense "cholestane-3β-ol, acetate of," comparable to estrone acetate, cortisol 21-acetate, cholestane-3β, 5α, 6β-triol 3,6-diacetate. An alternative method is that currently used by sugar chemists: O-acetyl-Δ⁵-cholestene-3β-ol. Our only contention is that the yl-system should be abandoned.

[11] The compromise scheme is stated on p. 889 of *Steroids*; it was added, in proof, too late for application in earlier parts of the book.

ERRATUM

J. JACQUES, C. WEIDMANN et LAM CHANH BINH: Structure moléculaire et activité oestrogène—XIX. Préparation stéréosélective des acides méthyl-2(méthoxy-6′-naphtyl-2′)-3 pentanoïques *thréo* et *erythro*, *Tetrahedron* **8**, 150–162 (1960).

The captions for Figs. 1 and 3 on pp. 152 and 156 of the above article should be transposed to read correctly.

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